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SOME QUESTIONS ABOUT BRONCHIOGENIC CARCINOMA*

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EVER since cancer has been subjected to surgical attack, neoplasms have constituted a problem that has been generally regarded as belonging especially in the province of the surgeon. But his interest in neoplastic disease has not been confined in the past, — nor should it be in the present, — to methods of resection of the growth. Many surgeons have made important contributions to the pathology, the peculiar actions, and even the etiology of some of the neoplasms. Percivall Pott of London, for example, at about the time of your "Boston Tea Party," was the first to call attention to the etiologic relation of an occupation to the formation of a cancer, in his writings on "chimney-sweeps' cancer." Here in Boston, Harvey Cushing and his associate, Percival Bailey, did much to elucidate our knowledge of differences in behavior of different types of brain tumor. Other examples could be cited. I, therefore, feel no need of apologizing for selecting as the subject of my lecture tonight some considerations of the etiology and behavior of bronchiogenic carcinoma. Moreover, as the title suggests, I shall raise a number of questions about this condition with the hope that perhaps answers may be found more readily if the problems are clearly understood.

The importance of the problem of bronchiogenic carcinoma is still not sufficiently appreciated. Perhaps many in this audience do not realize what an enormous increase has occurred in the incidence of the condition throughout the western world. Wherever vital statistics are available they have shown this tremendous increase. Doll and Hill[1] state that in the twenty-five years between 1922 and 1947 in England and Wales the number of deaths ascribed to this condition increased roughly fifteenfold. In the United States the annual death rate per 100,000 of the population from cancer of the lungs and pleura has shown the following rise: 1914 — 0.58; 1930 — 2.70; 1935 — 4.52.[2] In other words, in this country the increase in incidence was almost eightfold in the twenty-one years between 1914 and 1935. Judging from what has happened in other countries, one may assume that the incidence since 1935 has increased still further, although I have been unable to find the more recent statistics. Probably, therefore, the fifteenfold increase in England and Wales is not far out of line with what has occurred here. Unless this increase is checked it would seem that in ten, fifteen or twenty years the incidence of the condition will be truly alarming. The number of deaths reported annually by the United States Public Health Service from cancer of the lung has not yet reached that of deaths from cancer of the stomach, but the death rate from the latter condition seems stationary. Thus in 1930 the number of deaths from cancer of the stomach was 25,228, and in 1945 it was 25,832.[3] With the increase in population that occurred during that time, the increase of 600 in deaths does not represent a significant rise in the death rate. In 1945 the actual number of deaths reported as from cancer of "the respiratory system" was 13,882.[3] But nobody knows how many other deaths from this cause were reported erroneously as due to tuberculosis, lung abscess, atypical pneumonia and what not. In three different institutions in the country it has been discovered in recent years that the incidence of bronchiogenic carcinoma is actually higher than that of carcinoma of the stomach. The hospitals concerned are the Charity Hospital of New Orleans (Ochsner and DeBakey[4]), the St. Louis City Hospital (Saxton, Handler and Bauer[5]) and the Hines Veterans Hospital, of Hines, Illinois (Ariel and others[6]). These findings are significant because none of the hospitals mentioned receive a selected referred list of patients. Bronchiogenic carcinoma has, therefore, in a period of about thirty-five years, climbed from sixth to seventh place in order of frequency to one that rivals or possibly has passed carcinoma of the stomach for first place — at least in the male sex alone. This is a truly amazing phenomenon, which has no parallel in regard to any other cancer. It is so astounding that it must lead everyone acquainted with the facts to inquire about an explanation.

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Another remarkable feature of this condition is its overwhelming predilection for the male sex. When Adler[7] wrote the first monograph on this subject in 1912 the ratio of affected males to females was usually stated to be about 5 to 1. By contrast, in our last 150 cases the ratio was 18 males to 1 female. Mason,[8] in England, reported in 1948 that in 1000 cases the ratio of males to females was 9.2 to 1. Lindskog[9] found the striking fact that although in a series of 100 cases seen by him between 1938 and 1943 the ratio was only 4.5 to 1, in another series collected in 1947 and 1948[10] the ratio had increased to 24 males to 1 female.

Are there any possible explanations for these strange phenomena of the enormous increase of bronchiogenic carcinoma and the fact that it occurs much more frequently in male patients?

Let us discuss the last question first. So far as I know it has never been suggested that the female lung differs in any respect from that of the male, except perhaps in size. It would seem unlikely, therefore, that inherent sex factors could be responsible for the marked sexual disparity in the incidence of this cancer. Nevertheless, the idea was put to experimental test. Kemler and I[11] used Greene's[12] technic of transplanting fragments of tumor tissue into the anterior chambers of the eyes of guinea pigs. Briefly, it was found that either a well differentiated or an undifferentiated bronchiogenic carcinoma from a man could be transplanted with equal success into both female and male guinea pigs. Likewise, in an unpublished study, Gumbreck has found no appreciable difference in the amount of male sex hormone in men with bronchiogenic carcinoma from that in normal controls of about the same age.

It would seem, therefore, that we can dismiss the idea that there is any inherent sex factor that explains the greater frequency of this cancer in the male sex. Rather, it seems that a more appropriate idea might be that the people of the western world have exposed their lungs during the last thirty-five or forty years to some exogenous carcinogenic factor to a greater extent than previously and that men have been exposed to this factor more than women.

Several possible sources of this factor or factors suggest themselves at once. The first of them is petroleum products, for the use of the automobile began about coincidentally with the increase in incidence of bronchiogenic carcinoma. Although there is a slightly greater incidence of the condition in garage and oil-field workers, there is not enough to explain the enormous general increase.

If, however, we turn our attention to cigarette smoking as a possible source of a carcinogenic factor we find much evidence that incriminates that habit. Although some cigarettes were smoked in the last century, the extensive use of them on the present enormous scale began at about the time of World War I. Since then their manufacture and sale have increased at an almost incredible rate. For example, according to figures released by the Department of Agriculture,[13] 355 billion cigarettes were manufactured in this country last year. On the basis of a total population of about 150 million, that figure means that on an average every person, including babies, smoked 118 packs per year, or more than 6 cigarettes per day. These colossal figures seem to me to force one's attention to the possibility of a relation between the tremendous increase in cancer of the lung and the enormous consumption of cigarettes.

This possible relation has occurred to many during the last quarter-century. In fact, even as early as 1912 Adler[7] suggested that tobacco smoking might play a role in the etiology, although at that time he could collect reports of only 374 cases of bronchiogenic cancer from the world's literature. Later, Tylecote,[14] Hoffman,[15] Roffo[16] and Mueller[17] were some who produced some evidence prior to 1940 to indicate that smoking (especially of cigarettes) may be an important etiologic factor. In 1941 Ochsner and DeBakey[18] called attention to the similarity of the curve of increased sales of cigarettes in this country to that of the ascending prevalence of primary cancer of the lung.

These suggestions, however, were not generally accepted, because they were not accompanied by sufficient evidence. What was needed was at least a large-scale statistical study of cancer patients. In May of last year Wynder and I[19] published such a study, based on 684 proved cases. It is important to add that in all cases personal interviews were held and the interviewers, who were not physicians, used the same questionnaire. This is a matter of great importance, because hospital records and questioning of the families of patients are completely unreliable in investigations of this kind. As a result of our study, it was concluded that excessive and prolonged use of cigarettes is an important factor in the induction of bronchiogenic carcinoma. Of 605 men with lung cancer 51.2 per cent were "excessive" or "chain" smokers, as compared with only 19.1 per cent in a control series of 780 male patients in the Barnes Hospital of corresponding ages who did not have bronchiogenic carcinoma. By "excessive" smokers were meant those who had smoked from 21 to 34 cigarettes per day for more than twenty years; the term "chain" smokers was applied to those who had smoked 35 or more cigarettes per day for the same period of time. On the other hand, only 2 per cent of the men who had bronchiogenic carcinoma were nonsmokers. Smoking seems to play a similar but somewhat less evident role in the induction of epidermoid and undifferentiated carcinoma in women. By contrast, a greater percentage of nonsmokers was found among them than in men, with 10 of 25 female patients being nonsmokers. A frequently expressed criticism of

the idea that cigarette smoking may be an important etiologic factor is the contention that women smoke at least as much as men but have a much lower incidence of the disease. On the contrary, our study shows that women of the cancer age actually smoke much less than men and in general have smoked for much shorter periods of time. For the most part, the female heavy smokers are young women who have begun to smoke rather recently. For example, among 552 female patients at the Barnes Hospital without lung cancer between the ages of thirty and seventy-nine, 79.6 per cent were nonsmokers and only 1.2 per cent could be classified as "excessive" or "chain" smokers over a period of twenty years. Of all our patients with lung cancer, both male and female, who were smokers, 96 per cent had smoked for more than twenty years. Comparatively few women have smoked for so long a period. Long exposure to the carcinogenic influence of cigarettes seems necessary to produce the cancer. Perhaps, then, if the present-day young women continue to smoke as much as they do now, in another decade or so bronchiogenic carcinoma may have a much higher incidence in females than it has now. Of interest also is our finding that there may be a lag period of ten years or more between the cessation of smoking and the occurrence of the cancer. This finding is not out of line with what is known in the experimental production of cancer with carcinogens.

Simultaneously with our work, a similar study was being made in England and Wales by the well known statisticians Doll and Hill.[1] Our work was published in May; theirs, in September of last year. Their study also was based on a plan of personal interview by nonmedical interviewers in order to minimize the chance of bias. The similarity of the two studies and their results are remarkable. Our study[19] comprised 684 proved cases; that of Doll and Hill[1] included 709 cases. They found that of the men only 0.3 per cent, but of the women 31.7 per cent, were nonsmokers. The corresponding figures of nonsmokers for the non-cancer control groups were: men, 4.2 per cent and women, 53.3 per cent. "A relatively high proportion of the patients with carcinoma of the lung fell in the heavier smoking categories. For example, 26.0 per cent of the male and 14.6 per cent of the female lung-carcinoma patients who smoked gave as their most recent smoking habits prior to their illness the equivalent of 25 or more cigarettes a day, while only 13.5 per cent of the male and none of the female non-cancer control patients smoked as much." They state also that their figures suggest that "above the age of 45 the risk of developing the disease increases in simple proportion with the amount smoked, and that it may be approximately 50 times as great among those who smoke 25 or more cigarettes a day as among nonsmokers."

Another very important study relating to the possible etiologic relation of cigarette smoking to bronchiogenic carcinoma is a recent one by Dungal,[20] professor of pathology at the University of Iceland. He states that in 1939 autopsies performed at Reykjavik from 1932 to 1948 inclusive primary carcinoma of the lung constituted only 3.5 per cent of the total number of 337 cases of carcinoma of all sites. It stood ninth in frequency. He thinks that the probable explanation of its rarity in comparison with the incidence in other countries is to be found in the relatively small consumption of cigarettes in Iceland. For example, in 1932 the per-capita consumption was only 14 per cent of that in Great Britain. It remained low until the second World War, since which it has greatly increased, so that in 1947 the per-capita consumption was 4 times that of 1932.

It is not to be inferred that we regard cigarette smoking as the only etiologic factor in the production of bronchiogenic carcinoma. After all, in our study[19] 2 per cent of the men with the disease were nonsmokers, and in the study of Doll and Hill[1] 0.3 per cent of the men had not smoked. Furthermore, in our control group 19.1 per cent of the men had been excessive or chain smokers for at least 20 years without developing lung cancer. Nevertheless, the evidence that cigarette smoking has played an important role in the rapid increase of the disease seems very convincing. Pipe and cigar smoking apparently are less important than the use of cigarettes. It is possible that cigarette smoking has a synergistic influence on some other carcinogen, making it more effective in the production of the cancer in some manner, such as Berenblum's[21] finding that croton oil with resin greatly increases the effectiveness of some carcinogens in the experimental production of cancer.

Another consideration is the question whether or not some other exogenous carcinogenic factor besides cigarette smoking has been unusually prevalent during the period of rapid increase of bronchiogenic carcinoma. The well known high incidence of cancer of the lung among the Schneeberg miners is a striking example of the possible importance of occupational exposure. Are there any other occupational exposures or sources of large-scale air pollution that might be important in this respect? Wynder and I[22] have just completed a study of 857 proved cases with special reference to industrial exposures. Nothing dramatic or startling has come from the study. Nevertheless, it may be significant that the most frequently noted occupation was painting (6.1 per cent). The next most common group was hot-metal workers (5.8 per cent) and other metal workers (4.8 per cent), giving a total of all metal workers of 10.6 per cent.

From our own statistical study and from that of Doll and Hill, there seems to be an abundance of evidence to incriminate cigarette smoking as being

at least one factor in the etiology of most cases of bronchiogenic carcinoma. Final proof, however, will rest on the experimental production of the condition. We are now engaged in such work. It seems to me that the importance of obtaining direct experimental proof can hardly be exaggerated. No other cancer problem transcends this in importance, because of the terrifying rate of increase of bronchiogenic carcinoma and the clear lead to the possibility of arresting this increase that is furnished by the suggestive evidence of the etiologic importance of cigarette smoking. Many workers should be engaged in this problem, and every encouragement should be given them in their effort to establish the proof and, if possible, to discover the responsible carcinogenic agent.

Many attempts have been made in the past to produce malignant tumors experimentally by the use of tobacco products. Those studies made prior to 1941 have been well reviewed by Flory.[23] Roffo[24] claimed to have produced several carcinomas in rabbits' ears. Flory himself, in an extensive study, was unable to produce any true carcinomas in rabbits, but he did produce two squamous carcinomas in mice by painting them with tobacco tars. Perhaps a fair criticism of all previous work with tobacco could be that only those tars were used that were generally obtained by combustion of the tobacco at different temperatures and by collection of the distillates. Actually, the ordinary smoking of cigarettes is a different process — and adds the factor of combustion products of the cigarette paper. Arsenic, which is known to be a mild carcinogen, is present in paper in varying amounts. Also, one should consider that all tobacco is not the same. Some has been treated more extensively with insecticides than others. Many of the insecticides contain arsenic, and perhaps some contain other carcinogenic substances. Nevertheless, despite the relative infrequency with which carcinomas have been produced experimentally by the use of tobacco products, the evidence indicates that there is a carcinogenic factor in tobacco tars. The additional factor of the paper in cigarette smoking may explain why the use of cigarettes seems more likely to produce bronchiogenic carcinoma than the smoking of pipes or cigars.

By far the most common variety of bronchiogenic carcinoma is that which is usually designated as "epidermoid" or "squamous." Many tumors also are called "undifferentiated." In my own opinion, this latter type is usually only a variant of the former, as in many of the epidermoid cancers areas of undifferentiated cells are seen. In men, almost all tumors are epidermoid or undifferentiated. The type that is associated with excessive cigarette smoking is rarely anything else. One can therefore predict with a high degree of accuracy that a heavy cigarette smoker who has a bronchial carcinoma has one that belongs to the epidermoid type. Other tumors present the microscopical appearance of an adenoid arrangement of cells and are therefore called adenocarcinomas. Some pathologists recognize other varieties, which they designate as round-cell or oat-cell tumors, and still other names have been used to express differences in microscopical appearance.

It is well known that microscopical distinctions of cell types and arrangements are by no means absolute. Different parts of the same tumor and even different areas of the same microscopical section will often reveal variations that might lead one to assign different names according to what part of the tumor or section he might happen to be viewing. For example, occasionally the same tumor shows in some regions the typical findings of a squamous carcinoma and in other regions the characteristics of an adenocarcinoma. However, despite the comparatively rare diversity of appearance in different parts of the same tumor that might lead to a difference in classification, it is significant that by far the majority of bronchiogenic carcinomas in the male subject (94 per cent in our series) are those that would ordinarily be classified as epidermoid (or squamous) cancers, or a variant of that type called "undifferentiated." On the other hand, of the women of the series studied by Wynder and me, 35 per cent were diagnosed as having adenocarcinomas. It is perhaps significant that of the 39 men of our series with a diagnosis of adenocarcinoma 4 (10.3 per cent) were nonsmokers, a much higher percentage than that found for the epidermoid carcinoma (2 per cent). Also, of 13 women designated as having adenocarcinoma and 2 said to have terminal bronchiolar carcinoma 13 were nonsmokers and 2 light smokers.

It is apparent, therefore, that in general the "cigarette" cancer is almost always of the type commonly designated as epidermoid (squamous). On the other hand, the type that is usually called "adenocarcinoma" seems to have little if any relation to cigarette smoking. Also in the series of Wynder and myself there were 39 men with a diagnosis of adenocarcinoma and 13 women with that diagnosis, a ratio of only 3 men to 1 woman. It will be recalled that this small ratio is in marked contrast with the much higher ratio that is usually encountered for bronchiogenic carcinoma in general. From these facts it is tempting to conclude that the two most common histologic varieties of lung cancer, — epidermoid carcinoma and adenocarcinoma respectively, — are different diseases caused by the action of different carcinogenic factors. The increase in incidence of adenocarcinoma, if any, seems at most to be slight, although it is difficult to obtain satisfactory data on this point. There can be no doubt, however, that the type that is showing the alarming increase is the epidermoid or squamous. Other less common types recognized by some pathologists are the so-called round-cell

and oat-cell varieties. Still other names have at times been used. In my own opinion, little is to be gained by subdividing bronchial cancer into a large number of types based only on questionable morphologic differences in microscopical appearance and arrangement of cells.*

It seems to me that in the future, when our knowledge of the pathogenesis of cancer is more nearly complete, classifications will more likely be made on an etiologic basis than by microscopical appearance of the tumors. Only about a century or so ago it was customary for our forefathers to write learnedly of "the fevers," or to be content with making a diagnosis that the patient had a fever. Not until the discovery of, for example, the typhoid bacillus, the pneumococcus and the tubercle bacillus was it possible to have a clear comprehension of the differences in the fevers caused by the respective organisms and therefore to have a more rational understanding of the prevention and treatment of the diseases associated with those bacteria. Today our ignorance of specific carcinogenic factors tends to limit our concepts — and, therefore, our diagnoses of cancers — to morphologic and clinical classifications. Thus we say that a patient has a carcinoma of the stomach — and when we examine it microscopically we find it to be an adenocarcinoma. Perhaps the day will come when it will be said that the patient has the disease that is produced by such and such a specific carcinogenic agent. The dawn of a new day in that respect is already visible. The discovery by Bonser and her co-workers[25-27] of the remarkably high incidence of cancer of the urinary bladder in those who work for long periods with aniline is an example of the new period of a better understanding. I believe that the apparent etiologic relation of excessive cigarette smoking to the epidermoid cancer of a bronchus is another example. In neither case, of course, have the actual carcinogenic substances yet been discovered in a manner analogous to the discovery of the specific bacteria responsible for the fevers mentioned above, and it is by no means yet certain that only one carcinogen is the cause of either of the two examples cited. Yet in both cases I think no one can deny that more progress has been made toward a better understanding of the conditions than can come about by the futile and hair-splitting emphasis on a host of slight differences in morphologic appearances and arrangements of cells.

It is interesting to speculate on other differences of these two principal types of bronchiogenic carcinoma, with a consideration of their pathogenesis. It is admitted that much of the following discussion is highly theoretical, with few demonstrable facts — but is it inappropriate to use one's imagination?

*Perhaps the carcinoma that is generally called the "alveolar-cell type" is a fundamentally different variety from the others mentioned because of its similarity to the sheep disease known as "jagziekte." Limitation of time will prevent my discussing it here.

Whatever the carcinogenic factor or factors may be that are responsible for epidermoid cancer of the bronchus, it is clear that they transform the normal lining of cylindrical bronchial epithelium into flat or squamous epithelial cells at the site where the cancer begins. Such a transformation does not occur, for example, in cancer of the stomach; the cylindrical epithelial cells there are usually a conspicuous element of the typical adenocarcinoma of the stomach. It would seem, therefore, that the carcinogenic factors that produce epidermoid cancer of a bronchus have special qualities that differ considerably from those that produce the ordinary cancer of the stomach. Similarly, the adenocarcinoma of a bronchus seems to have a very different pathogenesis from the bronchial epidermoid cancer. As the name implies, it is characterized morphologically by the fact that the cells are arranged in such a manner as to suggest an attempt to form glands. Frequently cylindrical epithelial cells also are conspicuous. The origin of these tumors has been much discussed, and various possibilities have been suggested. An extensive presentation of the various views would be inappropriate in this lecture. However, I should like to discuss briefly the possible relation of this variety of bronchial cancer to the so-called bronchial adenoma.

In 1938 Womack and I[28] offered the suggestions that the so-called bronchial adenoma may be derived from a fetal bronchial bud that has remained dormant and that it is to be regarded as a potentially malignant tumor. Moreover, when the adenomas do become malignant they show the characteristics of tumors that are called by different pathologists adenocarcinoma, cylindroma, carcinoid, round-cell carcinoma, oat-cell carcinoma and so forth. Some of those who have been especially interested in this problem postulate that the adenoma arises in the bronchial mucous glands (Reisner,[29] Wessler and Rabin,[30] Fried[31] and Stout[32]). Others suggest that its origin may be in the epithelial cells of both the serous and the mucous glands of the trachea and bronchi or in the ducts of those glands (Goldman and Conner[33]). There has been no general agreement with our ideas, except that now almost everyone of experience admits that at least sometimes the adenoma takes on a malignant phase and may even metastasize to distant organs. We have never promulgated the idea that all the adenomas are malignant at the time they are seen and removed. We were careful to express the opinion that they are *potentially* malignant. It would seem, therefore, that that part of our conception, at least, has been found to be correct. Whether or not, when they do become malignant, they are as malignant or vicious as, for example, the epidermoid carcinomas is beside the point. Furthermore, it should be stated that the embryonic bronchial buds contain bronchial glands that might just as well be the origin of the so-called adenoma, as adult glands are. More-

over, nothing that has been said here would deny the possibility that some, perhaps even most, of the adenocarcinomas arise in adult glands. The main reason for my discussing this here is that it seems to me that there is plenty of evidence that at least sometimes a so-called adenocarcinoma arises in a so-called bronchial adenoma, and perhaps such a carcinoma may begin in a dormant fetal bud that has remained of microscopic size. Under such circumstances the carcinogenic agent has, in contradistinction to the case of the epidermoid cancer, acted on embryonic rather than adult epithelium. This suggests that it is a different agent and perhaps offers a clue to the reason that adenocarcinoma has not participated in the enormous increase that the epidermoid cancer has shown. I cannot terminate this discussion without referring to one champion of the ideas of Womack and myself, to whom we are duly grateful. Harris,[34] of the Department of Pathology of Tulane University, after a study of human fetuses and newborn babies, points out the similarity of infantile types of structures, especially the bronchial mucous glands and the peribronchial and peritracheal lymphadenoid tissue, to the histologic findings in bronchial adenoma. Since, in the material studied, the bronchial mucous glands occurred not only just beneath the mucosa but more deeply, between the cartilaginous rings, and since the lymphadenoid tissue was found not only peribronchially and peritracheally but within the walls of bronchi and trachea as well, Harris states that it can be deduced that tumors arising from such tissues may be intramural or extramural or may extend into the bronchial or tracheal lumen. In other words, they may show the "iceberg" character often seen in the bronchial adenoma. He also mentions the well known fact that adenomatous tumors have been found in childhood and refers to the article by himself and Schattenberg[35] in which several such tumors in children, one only seven days old, were reported. Finally, he states that his observations are compatible with the ideas of Womack and myself.

By this brief discussion it is not intended to imply that all the bronchial adenocarcinomas arise from remnants of fetal bronchial buds or from the so-called bronchial adenomas, but it does seem to us that at least some of them may have such an origin. The possibility remains, of course, that through the action of some carcinogenic influence the adult glands of the bronchi also may give rise to adenocarcinomas. Whatever the origin of those tumors may be, it would seem from the evidence briefly presented here that the carcinogenic factors responsible for them are different from those that are responsible for the more common epidermoid carcinoma. Moreover, it seems reasonable to suppose that the same patient may be exposed to the action of more than one carcinogen. This possibility may explain the occasional occurrence in the same person of the microscopical evidence of both epidermoid carcinoma and adenocarcinoma. Would this concept be materially different from, for example, our knowledge that a patient with tuberculosis can also develop typhoid fever or pneumococcal pneumonia?

One remarkable peculiarity about bronchiogenic carcinoma for which, so far as I know, there is not even a theoretical explanation is the fact that at autopsy metastases to one or both adrenal glands are found in a large percentage of cases. Dosquet[36] in 1921 commented on his finding of adrenal metastases in 21.8 per cent of his autopsies as compared with only 4.5 per cent in cases of carcinoma primary in other organs, and in 30 autopsies studied by Tuttle and Womack[37] in 1934 there were metastases in the adrenal glands in 33.3 per cent of the cases. Arkin,[38] in a study of 74 autopsies, found adrenal metastases in no less than 43 per cent. What can be the peculiar influence that attracts bronchial-cancer cells to the adrenal glands? So far as I know, there is no explanation of this curious phenomenon.

Perhaps I have taxed your patience with too much theoretical discussion. In closing, therefore, I should like to make a few remarks that pertain to the clinical aspects of the disease.

A distressing fact to the surgeon is that so small a proportion of patients with this condition reach him at a time when there is a good chance of eradicating the cancer by a suitable resection. In general this proportion is only about 25 or 30 per cent of the total number. One of the reasons is the delay of the patient in seeking medical consultation, but much too often the fatal delay can be charged to the physician who first sees him. Nearly 50 per cent of our patients have been diagnosed as having virus pneumonia before they reach us. A common chain of events is that when a patient consults his doctor because of a bad cough and perhaps the expectoration of blood-streaked sputum an x-ray film is made. On the film a shadow is seen that may represent some atelectasis or may not be characteristic of anything. Perhaps the patient has a little fever. By a process of wishful thinking the doctor diagnoses the condition as virus pneumonia. He prescribes some penicillin or another antibiotic. The patient loses his fever, develops a better appetite and generally feels better. The doctor is now convinced that his diagnosis of virus pneumonia was correct — and then the period of fatal delay begins. Unfortunately, he does not realize that bronchiogenic carcinoma, like other surface cancers, is usually accompanied by infection and that all he has accomplished with his antibiotic therapy is to combat a complication of the main trouble without affecting in the slightest degree the principal condition. Indeed, he may never have thought at all about the possibility of cancer, as he may be one of those physicians who still regard bronchiogenic carcinoma as a rare disease, something that

"can't happen here." Actually, it is questionable that true virus pneumonia is any more frequent than or as frequent as cancer of a bronchus. At any rate, a male patient of middle age or over who, without evidence of tuberculosis or bronchiectasis, begins to expectorate blood-streaked sputum should be suspected first of all of having a cancer. This is especially true if he has been a heavy smoker of cigarettes for twenty years or more. Indeed, such a patient can hardly fail to have a cancer. Proper steps should be taken at once to establish a diagnosis. Even if bronchoscopic and cytologic examinations fail to show positive evidence of cancer, he should have an exploratory operation. I feel certain that my friends in the audience who have had a large experience in dealing with this condition will agree with me in that recommendation.

If the surgeon has performed an exploratory operation and has found what seems to be a cancer, what shall he do then? If there is still doubt in his mind, it is nearly always possible safely to remove some tissue for a frozen-section diagnosis. In the great majority of cases, however, the surgeon who is experienced in dealing with cancer of the lung will have no difficulty in being certain of the diagnosis. Shall he then proceed with a total pneumonectomy or a lobectomy? It seems to me that the complete eradication of the cancer is more likely to be possible with pneumonectomy than with lobectomy because, — at least in my own experience, — better access is available to lymph nodes that may be involved. On the other hand, not much is gained for the patient if by eradicating the cancer we condemn him to spend the rest of his life as a miserable respiratory cripple so dyspneic that he can scarcely walk more than a few steps. All of us engaged in chest surgery have seen distressing results of that kind after pneumonectomy. The important paper of Churchill, Sweet, Soutter and Scannell[39] given last year before the American Association for Thoracic Surgery is very instructive, as in their series the percentage of survival for five years or more after operation was nearly the same in each of two groups of patients who had pneumonectomy and lobectomy respectively. Yet, important as these results are, coming from one of the best chest-surgery clinics in the world, the figures are hardly large enough to be statistically significant. Thus "there were 48 patients who had a pneumonectomy five or more years ago and of these, 6, or 12 per cent, survived five or more years. Similarly, there were 21 patients treated by lobectomy five or more years ago, of whom 4, or 19 per cent, survived five or more years." Overholt and Schmidt[40] reported in 1949 that of 41 resections performed five or more years previously there was a survival rate of 24.4 per cent. Our own figures for pneumonectomy are nearly the same as those of Churchill, Sweet, Soutter and Scannell for lobectomy and do not differ significantly from those of Overholt and Schmidt. In a study made in March, 1950, of 109 of our cases of total pneumonectomy performed prior to 1946 for carcinoma (exclusive of adenoma), 4 patients could not be traced, but 21, or 19.2 per cent, had survived a period of five years or more. I may add that the first patient to undergo a successful pneumonectomy for carcinoma is alive and well eighteen years after his operation, despite the fact that two lymph nodes were invaded by his epidermoid cancer. I do not have our figures for late survival after lobectomy only. Actually, however, it seems to me that none of us engaged in this work can form any satisfactory opinion of the effectiveness of lobectomy as contrasted with a pneumonectomy in obtaining a five-year survival until much larger series of comparative results can be obtained.

It seems to me reasonable to suppose that as time goes on the surgeon will not make his choice of pneumonectomy versus lobectomy by crude tests or merely by guessing whether or not the patient is likely to become a respiratory cripple, but will depend more on functional examinations of the lungs, which are far more accurate. The urologist has been far ahead of us for many years in his ability to determine whether or not it is safe to remove a kidney. Following the splendid example of Cournand, we have had at the Barnes Hospital for the past three years a laboratory equipped for such studies under the direction of Roos, a physiologist. Burford and I have found it to be of great value in helping us to decide in doubtful cases whether the patient should have a pneumonectomy or a lobectomy.

Summary

There can be no doubt that the incidence of bronchiogenic carcinoma has shown a great increase in recent years. In England and Wales it increased fifteenfold in the twenty-five-year period between 1922 and 1945. In this country the increase was about eightfold between 1914 and 1935. If the statistics for the years after 1935 were available they would probably reveal that as great an increase has occurred here as in England and Wales, since there has been a great rise in Great Britain since 1935.

By contrast the incidence of carcinoma of the stomach seems to be nearly stationary.

In several large hospitals in the United States bronchiogenic carcinoma has passed cancer of the stomach in frequency.

Although it is a disease that affects males much more often than females, the disparity cannot be explained by inherent sex differences. A bronchial cancer from a human male patient can be transplanted with equal facility into the eyes of guinea pigs of both sexes.

The evidence accumulated in both Great Britain and the Unites States indicates strongly that cigarette smoking is an important etiologic factor.

The commonly held opinion is fallacious — that if cigarette smoking is important the incidence of bronchiogenic carcinoma should be at least as great in women as in men, because of the popular belief that women in general smoke as much as men. A statistical study shows that actually there is a much higher percentage of women nonsmokers in the cancer age than men, and there is likewise a much lower incidence of women who are heavy smokers.

Two main types of bronchiogenic carcinoma can be recognized. These are the epidermoid (squamous) and the adenocarcinoma. Other types have received names, but most of them are probably variants of the two main types mentioned.

The epidermoid carcinoma and its undifferentiated variant are the ones that have shown the greatest increase. Likewise, it is this variety that is most prevalent in males and that is most commonly found in heavy smokers. On the contrary, the adenocarcinoma has apparently not shown much increase, is about equally divided between the two sexes and has a high relative incidence in nonsmokers.

It seems probable, therefore, that the cigarette cancer is the epidermoid variety and that this is essentially different from the adenocarcinoma in pathogenesis. Other fundamental differences are mentioned in the article. From this a concept is formed that the two main types of bronchiogenic carcinoma arise in response to different carcinogenic agents.

Doubtless the time will come when types of cancer will be differentiated on the basis of the carcinogenic factors that have induced them rather than by microscopical differences in cell structure and arrangement. Such a trend in classification will be analogous to the more precise diagnosis of the cause of a fever by recognizing that it has been the result of the tubercle bacillus, the typhoid bacillus and so forth.

The possible relation of the so-called bronchial adenoma to adenocarcinoma is discussed.

The high, and so far unexplained, incidence of metastases to the adrenal glands in cases of bronchiogenic carcinoma is mentioned.

The indications for lobectomy and pneumonectomy are briefly discussed. It is suggested that more use be made of preoperative tests of respiratory function in order to determine the advisability of total pneumonectomy.

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THE GENESIS OF CORONARY SCLEROSIS*

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WITH the increase in specialism there is a tendency for medical information to be contained in special compartments, so to speak. One of the most watertight compartments is that of pathology. Publication of its studies tends to be sharply limited to special journals. This is partly due to the desirability of concentrating pathologic records in special journals as the natural depositories of such data. It is also partly due to the tendency of clinical journals to look on papers dealing with pathologic questions as possibly too "technical" for their readers. However, there are certain fundamental matters that should be a part of the knowledge of every practitioner of medicine. The present paper deals with the steps in the evolution of one of the most important human diseases, — and more specifically with its development in the most critical site of its manifestations.

The literature is rich in illustrations of advanced coronary lesions. It lacks illustrations of the step-by-step progression of the developmental stages preceding full-blown coronary lesions. With a knowledge of what actually happens in the coronary artery undergoing sclerosis, the clinician should be better equipped to follow the development of the disease and to evaluate the therapy, preventive or other, that is offered.

In a general paper on atherosclerosis,[1] illustrations of coronary lesions from youth to old age were included. Among them were shown lesions in three coronary arteries that exemplified steps in the development of coronary sclerosis. This material was studied from a different standpoint from that of the present paper. Through the courtesy of the *Archives of Pathology* these illustrations, with comments on their significance, are presented for the information of clinicians.

In considering these lesions it is important to remember that cholesterol is constantly present in crystalline-ester form in the active lesions of atherosclerosis in man, as it is in experimental lesions of animals fed cholesterol, — rabbits,[2] chickens[3] and dogs[4] (with thiouracil). This is also the form in which cholesterol is found in the cells of the adrenal cortex, the interstitial cells of the testicle and the cells of corpora lutea. It is the form seen when tissues or cells rich in cholesterol (brain and cord, fat tissue or exudates) undergo necrosis. It is the form most commonly present in tumor tissues.

Crystalline esters of cholesterol occur almost exclusively within cells. When set free by the necrosis of cells they stimulate phagocytosis. The crystals (the fluid crystals of Lehmann) appear as spheroid drops or droplets, with the consistency of grease, but are rendered more fluid by heating. They take fat stains and exhibit maltese-cross images under polarized light. These characteristics are duplicated in the human body by esters of kerasin in Gaucher's disease and by esters of sphingomyelin in Niemann–Pick disease. These rare familial diseases are not likely to cause confusion. Moreover, when massed macrophages undergo rapid necrosis in human atherosclerosis because of inadequate nutrition and physical support, the esters are split and typical solid rhomboid crystals of cholesterol are precipitated, leaving no doubt about the sterol involved.

The liver is the principal site of cholesterol esterification.[5] In the rabbit, whether it is fed egg yolk, rich in cholesterol, solid crystals of cholesterol or crystals in solution in vegetable oil, the cholesterol is esterified in the liver. When produced in excess, ester crystals accumulate within the liver cells and constitute a burden. Kupffer cells in the liver sinusoids are the most important cells in the scavenger system of the body. Their standard function is the removal of particulate matter from the circulation. As the excess cholesterol crystals collect in the liver cells the Kupffer cells take on the function of their removal. The crystals are taken over in unit droplets, 1 to 3 microns in diameter, from the large drops in the liver cells, and are distributed evenly throughout the cytoplasm of the cholesterophages. When loaded, the Kupffer cells are set free at intervals from the liver sinusoids in showers, apparently by the release of a sphincter-like mechanism. They are carried by the blood stream to the lungs. They pass the capillary system of the lungs with ease, through their ameboid powers, arrive at the pulmonary veins still in shower grouping and are pumped into the systemic circulation.

Arterial blood flows rapidly in a zonal stream, — cells in the central zone and plasma in the peripheral zone. The lesions of atherosclerosis in man and in experimental animals tend to occur at selective sites, particularly the early lesions. These sites include the ascending aorta, the coronary arteries, the orifices of the aortic branches and the branching points of vessels. These sites correspond to points at which the zonal flow of the blood stream is interrupted,[6] that is, in the ascending arch by the closure of the aortic cusps, in the coronary arteries because the muscular branches are compressed by the contracting heart in systole and

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cannot receive blood, while the epicardial branches, the usual site of lesions, contain slowly moving blood. The main coronary flow is diastolic. Swirling currents arise at orifices of aortic branches, and branching points divide the blood stream. Interruption of zonal flow permits mingling of cells and plasma. The Kupffer cells can make contact with the intimal wall. These cells, studied by Rous and Beard,[7, 8] were found to be large cells with a capsule-like membrane capable of great enlargement to a diameter of as much as 100 microns. The cells were sticky and tended to cling to surfaces in cultures.

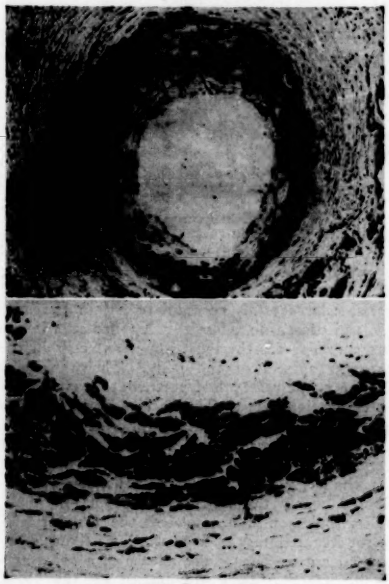

FIGURE 1. *Section of Anterior Descending Branch of Left Coronary Artery in Case 1.*
A = *old fibrous lesion being invaded by cholesterophages (x38).*
B = *detail of cholesterophages from lesion shown in A (x150).*

The cholesterophage — the Kupffer cell — can be caught in the act of invading the arterial intima in man and in the experimental rabbit.[1] It can be found clinging to the wall and lifting the edge of an endothelial cell to make a passageway, or may appear beneath a hump-like projection, covered only by an endothelial cell, beneath which it has escaped from the blood stream into the subendothelial layer of the intima. At points where a passageway has been opened other cells congregate, perhaps having entered the subendothelial layer by the openings established by earlier invaders. The accumulating cells produce lesions that, as they enlarge, become visible to the naked eye.

These steps in the production of lesions of atherosclerosis have been illustrated elsewhere.[9] They serve as an introduction to the study of the coronary lesions to be considered.

THE LESIONS

The lesions illustrated in Figures 1 and 2 were incidental findings in the bodies of persons who came to their deaths as the result of violence. In neither case were the collateral lesions or the history of significance with relation to the coronary process. On the other hand, the lesions illustrated in Figure 3 had a definite relation to the cause of death, and the history had significance.

CASE REPORTS

CASE 1. Figure 1*A* is from a frozen section of the anterior descending branch of the left coronary artery, fixed in formalin and stained with hematoxylin and Sudan IV. The lumen is markedly narrowed. There appears in the intima a collection of macrophages that stain deeply with the fat stain. This wave of cells lies wholly within the intima, as is shown by its clear inner fibrosed layer. Under higher magnification the cells seem to be held rigidly in ameboid form in the dense fibrotic tissue that they are invading (Fig. 1*B*). Their contents are granular; under polarized light they were identified as crystalline esters of cholesterol. Hints of an earlier wave are seen in the fragments of cells lying deeper in the intima about the active wave. These are probably remnants of macrophages in a wave that failed to penetrate deeply into the intima scarred by the repair of earlier waves of cholesterophages.

This lesion presents a single active wave of macrophages, with possible remains of a former now inactive wave.

CASE 2. In Figure 2*A* is reproduced a frozen section of the left coronary artery, fixed in formalin and stained with hematoxylin and Sudan IV. The eccentric thickening of the intima and the narrowing and distortion of the lumen are seen, as is the deep staining of the deeper layers of the intima by Sudan IV. Two layers of fat-staining material are suggested in this region. The inner portion of the thickened intima is made up of a loose-textured connective tissue. The media appears to be intact, though thinned in the lower segment in relation to the deeply stained portion of the intima. In Figure 2*B*, under polarized light two distinct bands of doubly refractive material are seen. The coarser band, near the media (II), is made up of solid crystals of cholesterol. In the relatively thick frozen section the crystals lie at various angles and on many planes, but following the sections through many planes left no doubt of the character of the crystals. The upper band, granular in Figure 2*B* (I), is seen in Figure 2*C* (I) to be made up of cells, largely ovoid, with granular contents. After the slide had been warmed, pressure was brought on the cover glass over this granular band; this led to the rupture of many cells, freeing their contents (Fig. 2*D*). The warm esters of cholesterol fused together to produce larger crystals. Remains of unruptured cells appear below, at the left.

This figure illustrates the presence in the coronary artery of two distinct layers of doubly refractive material, representing the results of two distinct waves of invasion of the intima. The older layer of cholesterol crystals represents the end results of a wave of macrophages that underwent sudden necrosis, with splitting of the esters and precipita-

tion of solid crystals. The interval between this wave and the formation of the more recent cell group was probably months. The delicate connective tissue marking the inner thickening of the intima apparently arose from the short

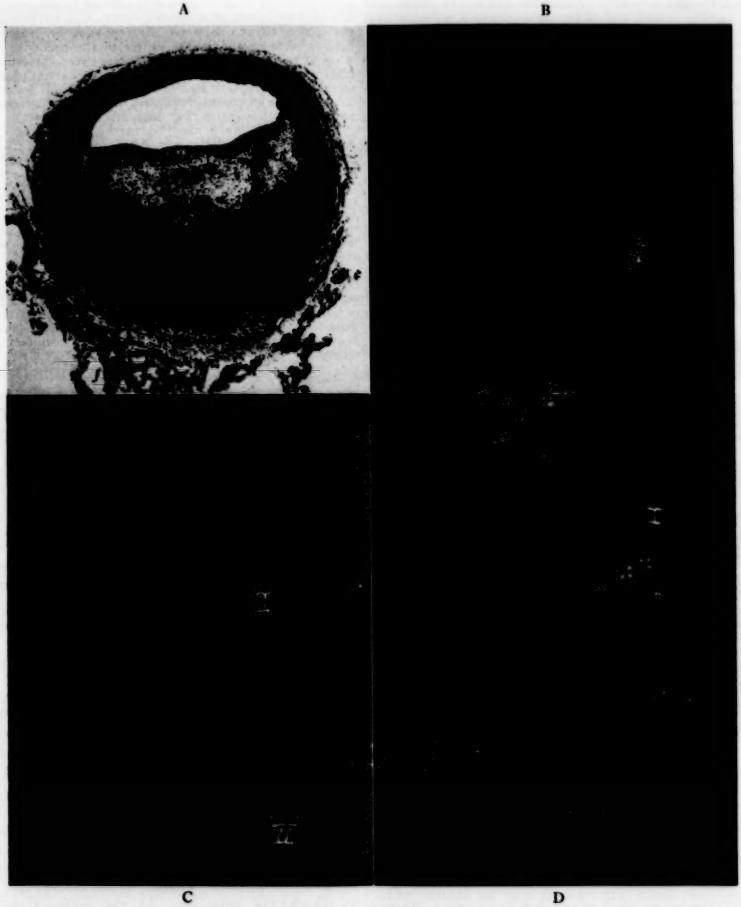

FIGURE 2. *Section of Left Coronary Artery in Case 2.*
A = early fibrosis near the lumen and fat-staining material in two layers below (x60). B = the same lesion as seen under polarized light (x60). C = enlargement of the two layers of doubly refractive material shown in B, under polarized light (x250). D = crushed area of a cell layer seen in C, under polarized light (x300).

stay of the wave of macrophages in the tissues as they traversed the tissue by ameboid motion from the point of invasion to the deep layers of the intima.

CASE 3. S. S., a 25-year-old man, suddenly felt a pain in the abdomen and collapsed. A rescue squad from the Fire Department used a respirator, without response. He was pronounced dead in a few minutes by his physician. He had suffered from indigestion for years, particularly in the two months prior to his death. He had been treated for gastric ulcer, although x-ray examination at a hospital had been negative.

Post-mortem examination revealed an obliterative pericarditis with no deep scarring. The heart and pericardium together weighed only 385 gm. The blood was fluid. The wall

of the left ventricle measured 1.6 cm., that of the right ventricle 0.65 cm. The mitral valve showed minor thickening of the anterior flap along the contact edge. The valves and cavities were otherwise normal. There was thickening of the wall of the left coronary artery, with considerable narrowing of the lumen. There were yellow deposits in the intima of the circumflex branch and of the right coronary artery without much thickening of the wall. The vessels were empty, with no suggestion of thrombosis.

Other organs were normal. There was no evidence of an active or healed peptic ulcer. There was no myocardial fibrosis. Search for Aschoff nodules gave a negative result.

Figure 3 was made from two sections of the left coronary artery at different levels. The tissue was fixed in Zenker's

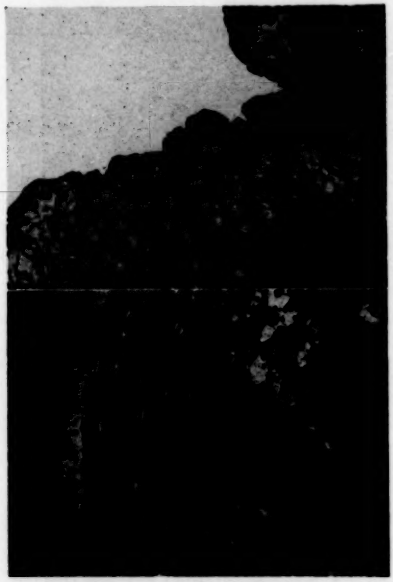

FIGURE 3. *Two Sections of Left Coronary Artery in Case 3, Taken from Different Levels.*

A = *early coronary lesion, showing cholesterophages with a delicate fibrous network* (*x300*). B = *moderately advanced coronary lesions* (*at right*), *with a fresh invasion of cholesterophages beneath the epithelium reactivating the advanced lesion at the left* (*x225*).

fluid and stained by Mallory's aniline-blue method. Three waves of macrophages are shown invading the coronary intima. In Figure 3*B* (I) the newest wave of macrophages is seen over the surface of a dense nodule at the left of the field. In this region two fibrosing nodules in the intima had narrowed the lumen to a slit. The granular macrophages in the wave at the left are literally lifting the endothelial layer from its attachments, save for a few slender bands of connective tissue. The second wave of macrophages, seen in Figure 3*A* (II), days or weeks older than the first, is made up of a broad band of cells enclosed in more orderly fashion in pockets in a fine mesh of connective-tissue bands. The pockets contain single macrophages or, in some instances, small groups of cells. The third wave is represented in the portion of the fibrosing nodule at the right in Figure 3*B* (3). The fibrous connective tissue, stimulated by the contents of the macrophages, is maturing. Broadening of the bands of connective tissue between them has crushed the macrophages, most of which have disappeared, having undergone necrosis due to cutting off of nutrition or to physical strangling in the dense tissue. Enough macrophages or fragments of macrophages persist in the center of the lesion to indicate what is taking place. The crystalline-ester cholesterol contents of the destroyed cells have disappeared, perhaps by metabolism. If death had not supervened, this lesion would have gone on to complete fibrosis, with disappearance of the excess crystalline esters that caused the lesion.

This case is particularly remarkable for the massive character of the second wave of macrophages. This type of macrophage invasion is rarely seen in the coronary arteries in man. It resembles the massive processes that are sometimes found in the rabbits daily fed large amounts of cholesterol. The left circumflex branch and the right coronary artery showed minor degrees of invasion by this wave. Also remarkable is the occurrence of Wave I so shortly after the massive Wave II. Wave III represents an invasion weeks or months before the sequence of Waves II and I.

The symptoms of indigestion in this patient were accepted as due to peptic ulcer. He had been on a Sippy diet on occasion in the past, and at all times his diet had been rich in milk and cream. This may account for the large amount excess cholesterol present in the macrophages in Wave II. Death was apparently due to coronary insufficiency.

Comment

In the coronary arteries of these three cases are shown six waves of macrophages carrying crystalline esters of cholesterol and the results of their activities. The lesions exemplify most of the steps in the evolution of atherosclerotic lesions, from very early deposits of invading cells in the subendothelial layer of the intima to fibrosis and scarring at the end. They include the effect of sudden mass necrosis of macrophages, with the precipitation of solid crystals of cholesterol, in one wave. The only stage not shown is the final complete scarring of lesions, or calcification, which follows or is associated with necrosis of tissues and is a terminal deposit, — literally a dead end.

The age sequence of the lesions, beginning with the earliest, is: Fig. 3, I; Fig. 3, II; Fig. 2, I; Fig. 1; Fig. 3, III; and Fig. 2, II.

The subject of advanced coronary artery lesions that cause immediate death is discussed and illustrated in an early paper.[10]

Discussion

The coronary form of atherosclerosis arises as the result of the intermittent invasion of the coronary intima by waves of macrophages carrying crystalline esters of cholesterol. The disease is chronic, except in the highly susceptible, years elapsing in most cases before repeated waves produce a critical lesion. The time intervals between the waves of cells may be days, weeks or months, frequently months in persons with no hereditary predisposition. The crystalline esters of cholesterol in the macrophages stimulate the growth of the connective tissue in which the cells lie. As the connective tissue matures it crushes the macrophages, cuts down the blood supply and causes necrosis of the cells, with dissipation of their cholesterol-ester contents. This leaves a fibrosed lesion.

In the study by French and Dock[11] of 80 young soldiers twenty to thirty-six years of age who died of coronary-artery disease, 91 per cent were overweight. Overeating had overwhelmed the human cholesterol metabolism, just as that of the rabbit

or the chicken is overwhelmed by ingestion of cholesterol or that of the dog by cholesterol with thiouracil. In actual fact atherosclerosis can be produced in experimental animals only by feeding cholesterol. The wholly artificial procedure of intravenous injection of colloidal cholesterol induces lesions that do not reproduce the lesions of atherosclerosis in human beings.

Thannhauser[12] says that herbivora should not be used for comparative experiments on cholesterol, as these animals cannot excrete cholesterol. In the rabbit, an herbivorous animal, it is possible to produce arterial lesions, through feeding cholesterol, that compare closely with the lesions of atherosclerosis in man. The first visible lesions in the aorta appear only after weeks of cholesterol feeding. By feeding many animals and killing certain ones at intervals during this latent period, it is possible to follow in detail the steps in the overpowering of the cholesterol metabolism, the deposit of the excess in ester form in the liver cells and the removal of the esters by scavenger cells that invade the arterial intima.

It is possible to prevent the production of atherosclerosis in the rabbit by feeding thyroid substance together with cholesterol.[13] It is not the inability of the rabbit to excrete cholesterol that leads to the experimental disease, but the lack of adequate thyroid control. On the other hand, the dog has such potent thyroid control that thiouracil (to damage the thyroid) must be added to the cholesterol diet in order to produce the disease. The influence of thyroid control is manifested in man by the minimal atherosclerosis seen in hyperthyroidism and the advanced atherosclerosis of hypothyroidism.

Removal of crystalline esters from cholesterophages already deposited in the arterial intima before permanent lesions have arisen, — particularly in infancy (diet) and at puberty (activity of sex hormones?), — is responsible for the near absence of atherosclerosis in youth.[14] At certain sites in the arteries of adults (for example, the ascending aorta), the removal of crystalline esters from early pinhead lesions generally prevents the development of advanced lesions. Experimental atherosclerosis in the rabbit is a curable disease. When feeding of cholesterol is stopped, the excess cholesterol is gradually removed from the organs and tissues, with restoration to normal, except in extreme lesions such as cirrhosis of the liver and nephrosclerosis.

Between the periods of deposit of excess cholesterol in waves in the coronary intima, the cholesterol metabolism functions sufficiently to prevent these deposits. It is hardly probable that sudden increases in the synthesis of cholesterol could account for the periods of excess. It is more probable that the source of the excess is the ingestion of excess cholesterol. The waves of cholesterophages are self-limited. The macrophages accumulate at the point of entrance in the subendothelial layer of the intima and then move in a body into the deep layers of the intima, where they stop as a unit. Invasion of the media is unusual. There are suggestions that the lesser waves are temporary in character. They could arise, perhaps, from excessive ingestion of cholesterol in a single day.

Man is practically the only mammal that is naturally subject to atherosclerosis.[15] A man who has suffered a coronary attack has demonstrated thereby his special susceptibility to the disease. If he survives he is treated for his acute condition and put on a low-cholesterol, low-fat diet to protect the rest of his coronary system against excesses of cholesterol.

Recent studies of blood cholesterol have indicated that men who have suffered coronary attacks tend to show a cholesterol level higher and less stable than that found in normal controls. They also apparently indicate that the blood-cholesterol level is not influenced by diet. From these findings has arisen a belief that a low-cholesterol diet is without value in the prevention or cure of vascular disease.[16] Some studies shed doubt on the validity of the blood-cholesterol test as a basis for unduly specific conclusions.

The findings of Gofman and his associates[17, 18] tend to shed further doubt on the value of blood-cholesterol tests as a measure of the functioning of the cholesterol metabolism. In blood serum subjected to the ultracentrifuge they observed the presence of a lipoprotein, containing 30 per cent cholesterol, at a flotation level of S_f 10-20, which had, apparently, a close relation to atherosclerosis. This lipoprotein had no essential quantitative relation to blood cholesterol. It was subject to the influence of low-fat diets that lowered the amount of the substance. This study also excluded chylomicrons, fat droplets found in serum after fatty meals, as a cause of atherosclerosis. The work of Gofman and his co-workers demonstrates that our knowledge of cholesterol metabolism is at present in a state of flux.

Conclusions

Atherosclerosis is a metabolic disease, comparable to diabetes. It is due to disturbances in cholesterol metabolism, which is apparently under the control of the thyroid gland.

The lesions of the disease are produced focally in the arteries by the deposit of excess cholesterol, in ester form within macrophages, at selective sites in the arterial intima.

Early human coronary-artery lesions show the intermittent waves of cholesterophages carrying excess crystalline-ester cholesterol into the arterial intima. The cholesterol esters stimulate growth of the connective tissue in which the cells lie. The maturing of the connective tissue at the expense of the cholesterophages leads to scarring. Repeated

waves of cholesterophages give rise to thickening of the coronary intima and narrowing of the lumen.

In the present state of our knowledge of cholesterol metabolism, low-cholesterol, low-fat diets are indicated in the treatment of persons susceptible to coronary-artery disease.

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RETROLENTAL FIBROPLASIA*

A Statistical Study with Particular Reference to the Effect of Vitamin A

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IN 1949 Kinsey and Zacharias[1] published a statistical study of retrolental fibroplasia. They discovered a sharp increase in the incidence of retrolental fibroplasia in their premature unit beginning in the year 1943, coincident with the substitution of a water-miscible multivitamin preparation for the Vitamin-D preparation previously used. They suggested that the large amounts of Vitamin A administered in this manner might play a contributory role in the production of the disease. Since Vitamin-A supplements are widely used in the feeding of premature infants, it became essential to investigate further the role of water-miscible vitamin preparations in retrolental fibroplasia.

In March, 1948, we had substituted a water-miscible multivitamin preparation containing Vitamin A for the aqueous Vitamin-D preparation we had been using.¶ In all other respects, our care of premature infants remained essentially unchanged.‖ We investigated the incidence of retrolental fibroplasia among the infants born during the fifteen months immediately prior to March, 1948, and compared it with our current incidence of the disease in order to evaluate the effect of the two vitamin preparations.

Since June, 1950, we have returned to the use of Vitamin D alone. The data collected from June, 1950, to October, 1950, are included in this paper, although the figures are too small to justify statistical analysis at present.

Procedure

All the infants reported in this study were seen at the age of six months or later. Eighty-nine per cent of the infants received a careful funduscopic examination under a mydriatic by an ophthalmologist. If the family had left town, we accepted letters from other physicians as evidence of normal vision (3 per cent of reported cases). When the parents refused to co-operate by returning to the clinic, a satisfactory examination by our social workers was accepted (8 per cent of reported cases). This consisted of checking grossly for vision and of examining with a flashlight the cornea, pupils, anterior chamber and lens. (The social workers were taught

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¶All infants received 20 minims of the multivitamin preparation beginning on the fifth day of life and continuing throughout their hospital stay. After discharge from the hospital the same preparation was often continued, but this was not subject to rigid control. The daily dose of 20 minims contained: Vitamin A — 10,000 units USP (as esters); Vitamin D — 2000 units USP (as activated ergosterol); thiamin — 2 mg., riboflavin — 2 mg.; ascorbic acid — 100 mg.; and niacinamide — 4 mg. Changes made by the manufacturer in the multivitamin preparation resulted in the following: After November, 1948, the daily dose of riboflavin was reduced to 1 mg. and the amount of niacinamide increased to 20 mg.; after July, 1949, the source of Vitamin A was changed from distilled natural esters to synthetic Vitamin A palmitate.

‖It might be well, for the record, to list briefly our routine in the Bellevue premature unit. Olac is used for feeding. Preliminary starvation lasts from twelve to seventy-two hours. Incubator care, including oxygen, is given to all infants under 3 lb. and to infants in poor condition, regardless of birth weight. The infant is kept in the incubator until he can maintain a stable body temperature and no longer needs oxygen. Vitamin K is administered at birth. Vitamin supplements are begun on the fifth day of life, as previously described. Elixir ferrous sulfate, 2 cc., is begun on the twenty-first day. Transfusions are used sparingly; the primary indication is a hemoglobin of 8 gm. or less.

the technic of this examination by the ophthalmologist.) It was planned that the ophthalmologist would check, — at a home visit if necessary, — any abnormal cases. However, no abnormal cases were discovered in this manner.

All infants diagnosed as having retrolental fibroplasia were examined by the ophthalmologist. The diagnosis of retrolental fibroplasia was based on the observation of a retrolental mass that had developed from changes in the vitreous and retina. In all instances the final picture was unequivocal.

It was often difficult to locate the infants at six months of age and to induce the parents to return them to the hospital for the necessary examination. In accomplishing this, the following routine steps were taken:

Letters were sent to the last available address notifying the parents of an appointment with their lists. This was a valuable check, as blindness is a reportable disease in New York State and entitles the parents to income-tax deductions.

Results

We are reporting in this study only those infants who received their final examination when they were at least six months old. We succeeded in obtaining such an examination of 81 per cent of the infants in the series who received Vitamin D and of 92 per cent of the infants who received the multivitamin preparation. As might be expected, the better follow-up was secured among those infants who had recently graduated from the premature unit.

In studies such as this, 100 per cent follow-up is nearly impossible to attain. It then becomes important to know whether the group followed is likely to be representative of the whole group. In the ophthalmologist. The reason for the examination was explained.

If the letters were unsuccessful, the social worker visited the address and attempted to persuade the parents to come to the clinic. If this failed, she examined the infant as described above.

If the family had moved, the social worker tried to obtain the address from the landlord or from neighbors. The post office and the local electric and gas-supply company were extremely helpful in providing us with forwarding addresses. Social agencies in whose care infants had been placed were also very co-operative.

Other major eye clinics to which cases of retrolental fibroplasia might be admitted were contacted. The State Commission for the Blind checked the names of our prematures against

Table 1. *Incidence of Retrolental Fibroplasia by Birth Weight (Avoirdupois).*

Preparation Administered	Under 3 Lb.			3-4 Lb.			Over 4 Lb.		
	Total Examined	RLF	Percentage of Incidence*	Total Examined	RLF	Percentage of Incidence	Total Examined	RLF	Percentage of Incidence
Vitamin D									
Nov. 46–Feb. 47	2	0	0	10	0	0	24	0	0
Mar. 47–June 47	4	0	0	12	0	0	24	0	0
July 47–Oct. 47	6	1	16.7	12	0	0	26	0	0
Nov. 47–Feb. 48	3	0	0	7	0	0	30	0	0
Totals	15	1	6.7	41	0	0	104	0	0
Multivitamins									
Mar. 48–June 48	4*	0*	0*	6*	0*	0*	29*	0*	0*
July 48–Oct. 48	2	0	0	7	0	0	35	0	0
Nov. 48–Feb. 49	5	1	20	15	0	0	28	0	0
Mar. 49–June 49	5	2	40	13	0	0	28	0	0
July 49–Oct. 49	6	3	50	8	0	0	43	0	0
Nov. 49–Feb. 50	4	2	50	14	1	7.1	30	0	0
Totals	26	8	30.8	63	1	1.6	193	0	0
Vitamin D									
Mar. 50–June 50	2*	1*	50*	19*	4*	21.1*	33*	0*	0*
July 50–Oct. 50	2	1	50	15	3	20	26	4	15.4
Totals	4	2	50	34	7	20.6	59	4	6.8

*Vitamin preparations were changed during this period so that some infants received Vitamin D and others received the multivitamin preparation.

reviewing our follow-up procedure, it can be seen that there is no reason to suspect that the incidence of retrolental fibroplasia would be any different in the group of infants missed from the incidence in those examined. The last step in the procedure (checking with other clinics and the State Commission for the Blind) might have resulted in a falsely high incidence of retrolental fibroplasia; however, no new cases were discovered through this means.

The results of our study are presented in Table 1. During most of our study, infants weighing over 5 lb. 4 oz. were not admitted to the premature unit. (Occasional exceptions were made.) The avoirdupois system is used to permit comparison with figures published by Kinsey and Zacharias. The study period was arbitrarily divided into four-month intervals in order to provide larger groups

for statistical calculations. In Table 2 the same data is presented with the infants divided according to birth weight by the more conventional metric system. It is important to have the material presented as such, as a means for comparison with future work. It also highlights some interesting information, as will be demonstrated later.

In both tables cases reported as retrolental fibroplasia represent only those infants who developed irreversible changes.

In Figure 1, the incidence of retrolental fibroplasia is graphed against time. The hump-like increase prior to the introduction of the multivitamin preparation represents only one case of retrolental fibroplasia. Study of this graph suggests several interesting points:

The incidence of retrolental fibroplasia appears to have risen during the course of our study, but the rise in incidence does not appear to be related to the utilization of the multivitamin preparation. This hypothesis was tested by the following statistical methods, using the group under 3 lb., since the most dramatic increase was seen in this group:

The period during which the multivitamin drops were administered was arbitrarily divided in half. The incidence of retrolental fibroplasia in the second half-period is significantly higher than in the first half-period.* If the introduction of multivitamin drops had been the factor that produced the increase, the rise in incidence would have been expected to occur at once, and there would have been no difference in incidence in the two half-periods. This was not true.

A regression line was drawn of the period of increased incidence of retrolental fibroplasia in the under-3-lb. group. The best-fitting straight line was used. The line has an upward slope, demonstrating an increasing incidence in retrolental fibroplasia.† If the multivitamin drops had been the cause of the increased incidence, a horizontal line starting abruptly at the point of introduction of the vitamin preparation would have been expected.

The porgressive involvement of the heavier weight group during our study, discussed below, would also be unexpected if the reason for our increased incidence were the introduction of the multivitamin preparation.

The incidence of retrolental fibroplasia varies inversely with the birth weight. To test this, the infants were divided into the following three groups according to birth weight: under 1500 gm., 1500-2000 gm., over 2000 gm. The incidence for the respective groups was 13/63, 7/177 and 3/268. Submitting these figures to the Chi-square test, it was found that the probability that the inverse relation of incidence to birth weight was due to chance was less than 1 in 1000.

During the course of the study, the heavier weight groups became progressively involved.

TABLE 2. *Incidence of Retrolental Fibroplasia by Birth Weight (Metric).*

	UNDER 999 GM.			1000–1499 GM.			1500–1999 GM.			2000–2499 GM.		
	TOTAL EXAMINED	RLF	PERCENTAGE OF INCIDENCE	TOTAL EXAMINED	RLF	PERCENTAGE OF INCIDENCE	TOTAL EXAMINED	RLF	PERCENTAGE OF INCIDENCE	TOTAL EXAMINED	RLF	PERCENTAGE OF INCIDENCE
Vitamin D												
Nov. 46–Feb. 47	0	0	0	5	0	0	11	0	0	20	0	0
Mar. 47–June 47	1	0	0	5	0	0	17	0	0	17	0	0
July 47–Oct. 47	1	0	0	5	1	20	19	0	0	19	0	0
Nov. 47–Feb. 48	1	0	0	4	0	0	9	0	0	26	0	0
Totals	3	0	0	19	1	5.3	56	0	0	82	0	0
Multivitamins												
Mar. 48–June 48	0*	0*	0*	6*	0*	0*	16*	0*	0*	17*	0*	0*
July 48–Oct. 48	1	0	0	4	0	0	9	0	0	30	0	0
Nov. 48–Feb. 49	2	1	50	7	0	0	17	0	0	22	0	0
Mar. 49–June 49	1	1	100	7	1	14	22	0	0	16	0	0
July 49–Oct. 49	2	1	50	5	2	40	15	0	0	35	0	0
Nov. 49–Feb. 50	1	1	100	7	2	29	16	0	0	24	0	0
Totals	7	4	57.1	36	5	13.9	95	0	0	144	0	0
Vitamin D												
Mar. 50–June 50	0*	0*	0*	4*	2*	50*	22*	3*	14*	28*	0*	0*
July 50–Oct. 50	0	0	0	5	2	40	19	3	15.8	18	3	16.6
Totals	0	0	0	9	4	44.4	41	6	14.6	46	3	6.5

*Vitamin preparations were changed during this period so that some infants received Vitamin D and others received the multivitamin preparation.

*The figures are as follows: In the first half-period there was one infant under 3 lb. with retrolental fibroplasia out of a total of 12 infants that were successfully followed. In the second half-period there were 8 cases of retrolental fibroplasia out of a total of 16 infants. Using Fisher's exact method,[5] because of the small figures involved, a probability of P = 0.024 was derived. This corresponds to a probability from Chi-square of 0.048. Taking figures less than 0.05 as significant (0.05 is equivalent to a chance incidence of 1 in 20), the difference in incidence is significant by a small margin.

†The strength of the relation between time and incidence was shown by a correlation coefficient of + 0.91, which is highly significant (a chance incidence of less than 1 in 100).

The incidence of retrolental fibroplasia was tabulated according to the following birth-weight groups: under 1000 gm., 1000-1499 gm., 1500-1999 gm. and over 2000 gm. The results were graphed against time, using a four-month interval in the same manner as demonstrated in Figure 1. The incidence rose first in the under-1000 gm. group, next in the 1000-1499-gm.

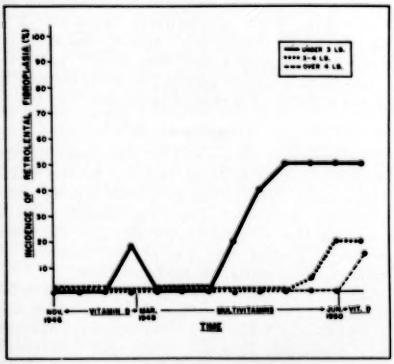

FIGURE 1. *Incidence of Retrolental Fibroplasia (Derived from Data in Table 1).*

The recent increased incidence and the progressive involvement of the heavier-weight groups are shown.

group and so on. The chance probability of this occurring in precise sequence is 1 in 24.

A spot graph was made of the period of increased incidence, as shown in Figure 2. In this figure, each dot represents a normal infant and each circle represents an infant with retrolental fibroplasia. The graph suggests that as time progresses the heavier-weight groups are being involved, although the character of the population, by birth weight, remains unchanged.

Because of a shortage of computing assistance, the more difficult method of fitting a regression line to test this hypothesis was not used. Instead, the following method, which is cruder but adequate, was employed: The period under observation was divided in half. The proportion of normal infants weighing more than 1500 gm. against those weighing less than 1500 gm. in the first half-time was compared to that in the second half-time by the Chi-square method. No significant difference was found; hence no gross change in the character of population by birth weight was indicated. Then the proportion of infants with retrolental fibroplasia in each category was compared in a similar fashion. This demonstrated a significant increase in the number of infants with retrolental fibroplasia in the over-1500-gm. group in the second half-time. This was checked by Fisher's[2] exact method.

Discussion

Before discussing our results, it would be worth while to review briefly the figures of Kinsey and Zacharias. These investigators compared the incidence of retrolental fibroplasia in the Boston

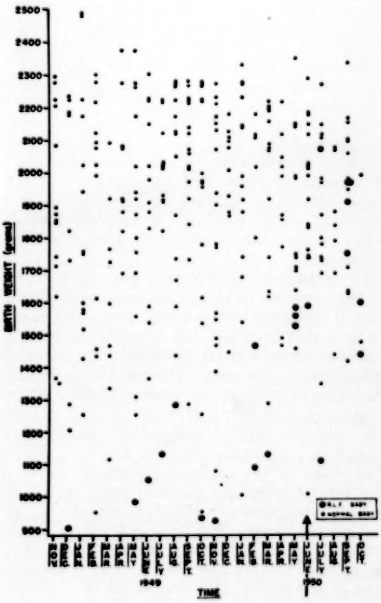

FIGURE 2. *Period of Increased Incidence of Retrolental Fibroplasia.*

Each dot represents a normal infant; each circle, an infant with retrolental fibroplasia.

Lying-in Hospital in the years 1938-1942 with the incidence in the years 1943-1947. In the group under 3 lb. they noted wide swings in incidence from year to year, ranging from 0 to 50 per cent. These yearly variations were attributed to the small number of infants in this group. There was no significant difference in the averages of the two periods. In the 3-to-4-lb. group, among 102 infants born prior to 1943, there was only 1 case of retrolental fibroplasia (1.7 per cent). However, in

this same weight group, between 1943 and 1947, 33 cases of retrolental fibroplasia developed among 162 infants (20 per cent). In their search for some factor to correlate with this significant increase they discovered only 2 major changes in the care of premature infants. These were introduced in 1943; the dosage of iron was increased and administration of a water-miscible multivitamin preparation containing Vitamin A was begun.

In our study, the dosage of iron was unchanged. The only change in therapy was the substitution of a water-miscible multivitamin preparation containing Vitamin A for an aqueous Vitamin-D preparation.* During the course of our study the incidence of retrolental fibroplasia has risen. However, it was over a year after the introduction of the multivitamin preparation that the increased incidence became apparent. It is therefore improbable that the new vitamin preparation, including the suspect Vitamin A, played any role in the increased incidence. Now, at the time of writing this paper, it is eight months since we have returned to the use of Vitamin D alone, and our incidence of retrolental fibroplasia appears to be remaining high. However, we do not have a complete six-month follow-up on enough infants to permit a definite statement.

The experience in our premature unit provides strong support to the current impression that the general incidence of retrolental fibroplasia may be rising — that hospitals that formerly enjoyed a low incidence of retrolental fibroplasia are at present seeing many more cases. During the course of our study, we have made the transition from a hospital of low incidence to one of relatively high incidence. This increase, in the absence of any important change in therapeutic regimen, makes it doubtful that many of the currently suggested factors are important etiologically. Among these factors may be listed dehydration,[3] anemia,[4] exposure to light,[5] and supplementary iron.† As a result of a recent investigation of incubators, we are using oxygen far more effectively now than we did at the beginning of the study. However, some of the heavier infants who developed retrolental fibroplasia were never placed in incubators. We also study our infants' eyes far more intensively and have given more than passing thought to the possibility that this manipulation may play a contributory role. We cannot adequately evaluate these factors on the basis of this study.

Our results conform with the experience of others in that the incidence of retrolental fibroplasia varies inversely with the birth weight. This indicates that the heavier infants are less susceptible. As the incidence in our unit has increased, the heavier weight groups have been progressively involved. This suggests that as the agent (or agents) that produces retrolental fibroplasia becomes more prevalent it also becomes more potent. It is interesting to speculate about what type of agent that may be.

*It is worth noting that Olac supplies 6000 units of Vitamin A in the form of halibut-liver oil per 100 gm. of powder (personal communication, Warren M. Cox, Jr., of Mead, Johnson & Company, April 24, 1951). This would supply the infant on an average formula with about 3000 units per day. However, since Olac was used routinely throughout the study, it does not seem possible that this could affect either our results or their interpretation.

†Kinsey and Zacharias also suggested that the administration of iron in high doses might have contributed to the sudden increase in incidence of retrolental fibroplasia noted by them. In their evaluation of the role of iron, they arbitrarily classified ½ dram or more of elixir ferrous sulfate per day as a large dose (personal communication, V. E. Kinsey, March 16, 1950). Anything below that amount was considered low. In our unit, ½ dram (2 cc.) of elixir ferrous sulfate is administered daily beginning on the twenty-first day.

Summary

The incidence of retrolental fibroplasia in the premature unit at Bellevue Hospital for the period of November, 1946, to October, 1950, is presented.

Between November, 1946, and March, 1948, a water-miscible Vitamin-D preparation was used routinely. During this period the incidence of retrolental fibroplasia was extremely low.

Beginning in March, 1948, a water-miscible multivitamin preparation containing Vitamin A was substituted for the Vitamin D. The incidence of retrolental fibroplasia remained unchanged until May, 1949. This persistently low incidence for over a year makes it very unlikely that the Vitamin-A preparation is a factor in the production of retrolental fibroplasia.

Since May, 1949, the incidence of retrolental fibroplasia has been rising. As the incidence has risen, the infants with higher birth weights have become involved.

The rise in incidence occurred despite the fact that our practices concerning transfusions, supplementary iron, exposure to light and the initial starvation period remained unchanged.

The hospital's social workers, Miss Lillian Green, Miss Shirley Cohen and Mrs. Lucille Boorstein, are responsible for the success of our follow-up study. Dr. Donald Mainland provided us with valuable advice and guidance in the statistical analysis of our results.

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WOOL AS A CAUSE OF ECZEMA IN CHILDREN*

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THERE are many children affected with eczema who are nearly or entirely free from it in summer but in whom it recurs at the onset of cold weather and lasts through winter and spring. As soon as the weather becomes warm their condition begins to improve. It is obvious that something harms them in winter that is absent in summer.

Wool deserves consideration as one possible cause. This has been noted by several observers.[1-4] Young children are veritably smothered in wool in the winter. They wear mittens, coarse snow suits, wool hats, sweaters, scarfs and socks; they are continually in contact with wool. The distribution of the eczema in these cases favors the front of the neck, the ankles, the wrists and the backs of the hands, arms and legs. The trunk and face are not commonly involved. The eczema is chronic or subacute rather than acute. The mother often knows that contact with wool, particularly if it is wet (mittens, snow suits), will produce it. When such an eczema has once started, it is aggravated and continued by incessant rubbing and scratching, so that it finally attains what the Germans have so aptly called "Selbständigkeit" — that is, it persists in its own right because of the chronic pathologic changes that have been produced in the skin, irrespective of further contact with the allergen. Eczema may also appear on parts of the body that are not in contact with wool, probably by absorption of the allergen from abraded areas or, possibly, from its inhalation.

Wool sensitivity of such high degree that urticaria is produced by only slight contact can occur, but it is uncommon. As a rule the degree of sensitization is not high; continual exposure and rubbing are necessary to produce any reaction. Positive scratch reactions to wool are uncommon. In a series of 300 eczematous infants and children, only 9 gave positive tests.

In the present study 40 children between the ages of two and twelve years were studied. Most of them were more severely affected in the winter; some were affected all the year. Scratch, patch and intracutaneous tests with wool were performed in all cases. For intracutaneous testing a wool extract containing .01 mg. of nitrogen per cc. was used. This is somewhat weaker than the usual extract used for intracutaneous testing (.10 mg.); it was employed in this strength in order to avoid as far as possible the nonspecific reactions that so often occur with the use of concentrated extracts. The technic of patch testing was as follows: A small area on the upper arm was gently scraped with the end of a tongue depressor in order to remove at least a part of the protective keratin layer. Then a small piece of a white all-wool blanket was applied *wet*, covered with the usual cellophane-and-adhesive patch, and was allowed to remain for a week. It is particularly important that the wool patch be kept in place for several days; an application of only twenty-four hours, such as is commonly used in patch testing, is not so likely to give a positive test.

Positive reactions were very definite; they consisted of erythema, fine crusted vesicles and papules. There were no bullous reactions, such as may be seen at times in patch tests with metals, dyes or other chemicals.

There was no relation between positive patch and intracutaneous tests; either might occur in the absence of the other. Five patients gave both positive intracutaneous and patch tests, 5 gave positive intracutaneous but negative patch tests and 9 gave positive patch but negative intracutaneous tests. All positive patch tests were of clinical significance; the significance of the positive intracutaneous tests was doubtful. There were no strongly positive intracutaneous tests.

TABLE 1. *Results of Scratch, Intracutaneous and Patch Tests with Wool.*

	SCRATCH	INTRACUTANEOUS	PATCH
Positive	0	10	14
Negative	40	30	26

It is certain that sensitivity to wool is not responsible for all cases of "winter eczema" in children. House dust is the cause in some of them; others cannot be satisfactorily explained in any way in the light of our present knowledge. Wool sensitivity is a common cause and is the easiest one to demonstrate.

TREATMENT

Avoidance of wool contact is not easy for children in the winter. Local treatment with appropriate salves or pastes and avoidance of contact not only with the allergen but with any external insult whatsoever, whether chemical or mechanical, are of paramount importance, and it is impossible to obtain good results unless the areas of eczema are protected at all times. Eczema in children generally begins mildly and is aggravated and kept

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active by continued external trauma; most of what one sees on the skin is caused by what the child does to himself.

Over whatever local medication is used is spread a piece of soft white cotton cloth (never gauze); the part is then snugly bandaged with several layers of 2-inch elastic bandage. This applies particularly when there is subacute or chronic eczema in front of the elbows, in back of the knees or on the wrists and ankles. If it is acute and weeping, this must be controlled by appropriate measures before bandaging. Ordinary bandages are useless; a thick elastic bandage is necessary, and it must remain in place twenty-four hours a day. It is a waste of time to treat such eczema in these children unless the parts are bandaged in this way. If the hands are involved, whatever salve is being used is applied at night and white cotton gloves are worn, — or in smaller children a white cotton stocking is pulled on over the arm so that the hand is in the toe of the stocking and the base of the stocking is pinned to the shirt or pajamas. During the daytime when out of doors the child wears leather mittens lined with cotton. Most children rebel at wearing white cotton gloves to school. Snow suits of rough woolen material should not be worn; they are poison to these children. "Byrd-cloth" or rayon snow suits with cotton lining are suitable. Wool sweaters, skirts and trousers may be worn if the skin is completely covered with cotton so that the wool clothes do not come into contact with it. A white cotton scarf is worn around the neck. Boys, as a rule, do not have eczema of the neck; the front of the neck, which is the most vulnerable part, is protected by the shirt. Wool eczema of the front and sides of the neck is more common in girls. At present white "turtle-neck" cotton jerseys are fashionable; they are excellent for these girls, as the "turtle neck" affords protection to the skin.

It seems likely that these patients' eczema is caused mostly by contact. It is possible, however, that the inhalation of wool may play a part. The blankets should be between sheets and the bedroom kept as free from wool particles as possible.

Hyposensitization

Little is found in the literature concerning attempted hyposensitization to wool. It has doubtless been reported many times, but the only report I have found is that of Lord.[1] He reported 4 patients, 2 with urticaria from wool and 2 with eczema. Hyposensitization was carried out for 2 of these patients with excellent results. I have only occasionally attempted hyposensitization with environmental allergens in eczema (atopic dermatitis), because there is so much difference of opinion concerning it, so few really accurate statistics, and so much chance, if a slight overdose is given, of aggravating the condition. Furthermore, since it is often difficult to obtain supervision for the other children in a family when one child must be brought in week after week for inoculations, such an undertaking is a major problem for any mother, aside from the expense involved. For these reasons I did not attempt what seemed to me a rather doubtful and often unjustifiable therapeutic procedure in most of the 14 cases of wool eczema reported; they progressed fairly well with local treatment and avoidance, as far as possible, of wool.

For 3 patients, however, hyposensitization was attempted. These 3 girls had such severe eczema each winter that it was incapacitating. In all 3 the condition was clearly caused by wool.

Case Reports

Case 1. P. M., a 5-year-old girl, was first seen on February 28, 1946. Her eczema had begun in her infancy, and she had never been entirely free from it. In the summer of 1945 the condition was very mild. As soon as the weather began to be cold (October) it recurred and became progressively worse, so that at the time of examination there was an extensive subacute eczema of the lower third of both legs, the popliteal spaces and the wrists. Sixty scratch tests with the usual environmental and food allergens were negative. An intracutaneous test with wool (.01 N) was negative. A patch test with wool was positive. She was treated with various salves, bandaging and avoidance of wool, and for the rest of the winter was fairly well. She had practically no eczema during the summer of 1946, but it recurred as usual in the fall. She was seen on March 3, 1947. At this time there was severe chronic eczema of the ankles, lower legs and arms, and in the popliteal spaces it was cracked and oozing to such an extent that she could barely walk and had to be hospitalized for about a week. Weekly inoculations were begun on April 10, 1947, with .10 cc. of a 1:10,000 wool extract as the initial dose. On May 7, .05 cc. of a 1:1,000 dilution was given. In about twenty-four hours there was a marked flareup of all the previous eczema, and a lichenoid eruption somewhat resembling an "id" eruption appeared all over the body. This disappeared in about 3 days, and the eczema reverted to its previous status. The condition was clearly an acute dermatitis produced by an overdose of the antigen. The next dose was reduced to .20 cc. of the 1:10,000 dilution,* and no further increase was made. Great improvement was noted. This small dose was given weekly until June and every 2 weeks thereafter during the summer of 1947 and the winter of 1947-1948. For the first winter in her life the patient had almost no eczema. Inoculations were discontinued during the summer of 1948 and resumed in October. During that winter she had very little eczema. Inoculations were started again in October, 1950, and the dosage was increased to .30 cc. of a 1:1,000 dilution. She was seen February 21, 1951, and given the usual inoculation. There was very slight eczema. Because of illness she did not return for treatment until March 21, at which time a great deal of subacute eczema was noted — on the back of the knees, in front of the elbows and around the wrists, — more than she had had since inoculations were started in 1947. Weekly inoculations were resumed, and in 3 weeks the eczema had almost cleared.

Case 2. N. S., a 20-month-old girl, had had eczema since the age of 5 months. Skin tests showed slightly positive reactions to wheat and to house dust. Omission of wheat and of several other foods from the diet was of no help.

She was not seen again for 7 years (April, 1947). During this time she had been nearly free from eczema in the summer, but it had always recurred each fall and persisted until the return of warm weather. There was a severe chronic eczema on the backs of the hands, the arms and the front of the neck.

*In hyposensitization with any environmental allergen in atopic dermatitis it is always desirable to keep the dosage low, as these patients cannot tolerate the dosage that would be used in respiratory allergy.

Scratch and intracutaneous reactions to wool were negative. A patch test was markedly positive. With local treatment and avoidance of wool the condition gradually improved, the skin was nearly clear by June, and the patient was comfortable during the summer as usual. In the early fall of 1947 weekly inoculations with wool were started (.20 cc. of a 1:10,000 dilution). Her condition during the winter of 1947–1948 was better than it had been for several years. There was some eczema but none of marked degree. Inoculations were discontinued during the summer of 1948 and resumed in the fall, with good results. Inoculations were given during the next 2 winters. The patient had a very moderate amount of eczema each winter, but it did not trouble her and was never so serious as it had been in the winters before inoculations were given.

Case 3. E. P., a 15-year-old girl, had had eczema during the winter on the arms and around the neck for 5 years. In the summer she had practically none. She also had mild hay fever, caused by grass pollen. She knew that contact with wool gave her eczema. She also knew that contact with or proximity to kapok gave her eczema, but she easily avoided this.

Scratch tests were positive to orchard grass, timothy, ragweed and kapok and negative to wool. A patch test with wool was positive. Inoculations with wool extract were begun in the early part of the winter of 1949 and continued weekly until May. The dose was .20 cc. of a 1:10,000 dilution. That winter she had almost no eczema. When seen in May she had none. Inoculations were also given during the next winter, with the same results. During the following winter she had no inoculations, and her condition was about the same as it had been in the previous 2 winters when she had been given inoculations.

Discussion

I am by no means prepared to conclude from such a small experience that wool hyposensitization is of value in eczema due to wool. A large series of cases, which would be almost impossible for any one physician to obtain, would be necessary before any valid conclusions could be drawn. I should be willing to say only that it is worth a trial, if the eczema is severe enough to warrant it.

Almost all these children with wool eczema would be classed as "atopic" children; that is, there is a high incidence of allergy in siblings and parents, they may have hay fever or asthma in addition to the eczema, most of them have had infantile eczema, and they give positive wheal reactions to various allergens such as pollens or foods, which may or may not contribute to the eczema. Their "eczema" is atopic dermatitis. Many of them, however, have no urticarial type of sensitivity to wool, and if they do have it it is as a rule of slight degree, so that the intracutaneous test is necessary in order to demonstrate it. The skin sensitivity is *superficial* and is determined by the patch test, which reproduces the lesion of the disease — dermatitis. It may well be that the sensitization is chiefly of the epidermis, but it seems certain that the most superficial papillary loops are involved as well, for the epidermis contains no blood vessels and erythema and papulation must of necessity come from vascular participation in the reaction. So I prefer to speak of such sensitization as "superficial" rather than "epidermal." The urticarial reaction takes place in the corium, and it must be remembered that with the intracutaneous test the test material is injected not into the most superficial but into the midparts of this layer.[5] It is not possible to *inject* anything into the epidermis; it is too thin.

It is commonly taught that the skin sensitization in atopic dermatitis is deep and that on testing it is demonstrated only by wheal reactions. A sharp line has been drawn between atopic and contact dermatitis. Perhaps this differentiation has been too sharp, for in atopic dermatitis there is sometimes a superficial as well as a deep sensitization, which can be determined by the patch test, well demonstrated by the patients reported here. An excellent discussion of this combined dermal and epidermal sensitization is given by Templeton.[6]

In a few of these cases no deep sensitization to any allergen can be demonstrated. Occasionally it is impossible, therefore, to make a sharp distinction between atopic and contact dermatitis. It is generally agreed, however, that sharp differentiation is usually warranted. If in atopic dermatitis there is a superficial sensitization, with a positive patch test, to the same allergen that causes a wheal with the scratch or intradermal test, it is probably best to call such cases "atopic dermatitis by contact."

Summary and Conclusions

"Winter eczema" caused by wool is common in children.

There may be combined deep and superficial sensitization or superficial sensitization alone.

Etiology is best demonstrated by the patch test.

In severe conditions, clearly due to wool, trial of hyposensitization is worth while.

Although classical "contact" and "atopic" dermatitis have enough immunologic and clinical differences to warrant their separation in classification cases that combine elements of both are not uncommon.

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MEDICAL PROGRESS

BLOOD GROUPING, BLOOD BANKING AND BLOOD TRANSFUSION (Continued)*

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TRANSFUSION THERAPY

Transfusions of whole blood, red-cell suspensions, plasma and plasma fractions are designed to serve one or more of the following objectives: restoration of the blood volume after hemorrhage, trauma and burns; maintenance of the concentration of circulating hemoglobin at an adequate level in certain types of anemia; provision of specific clotting factors that are lacking in patients with certain hemorrhagic disorders; reinforcement of the natural immune mechanisms by supplying specific antibodies in donor blood; restoration of the colloid osmotic pressure of plasma to physiologic levels in cases of hypoproteinemia; provision of protein nutrients in cases restricted to parenteral feeding; and, finally, the removal of blood possessing pathogenic properties and its replacement with normal blood.[8, 9] Although additional therapeutic benefits have been ascribed to blood transfusions, — for example, in cases of acute poliomyelitis,[10] — their value and therapeutic rationale in these conditions remain unproved.

The following section is devoted to problems of unusual importance relative to the conduct of blood transfusions in particular clinical situations:

The term "whole blood" as employed in this discussion refers to donor blood that has been collected in ACD (acid-citrate-dextrose) diluent and stored at temperatures between 4 and 8 degrees C. for periods of twenty-one days or less. A "red-cell transfusion" refers to injections of packed erythrocytes prepared by removing 60 to 80 per cent of the plasma from blood after spontaneous or mechanical sedimentation of the red cells. Prior to injection a red-cell concentrate may be diluted with chilled saline solution (0.85–1.0 gm. per 100 cc.) in order to reduce the viscosity and thereby facilitate the injection.

"Plasma transfusions" refer to injections of the cell-free portion of whole blood collected in ACD diluent or in trisodium citrate solution, the formed elements having been separated by a process of spontaneous or mechanical sedimentation and the plasma supernatant removed by aspiration. Plasma that is distributed from commercial sources is prepared by pooling numerous donations in order to reduce the concentration of anti-A and anti-B isoagglutinins. After exposure to ultraviolet irradiation, designed to eliminate the risk of virus infectivity, which is increased by pooling, the product is desiccated and packaged in readiness for use. Accompanying each vial of dried plasma is an ampoule of sterile distilled water sufficient for reconstitution, the concentration of protein and other solutes in the reconstituted material approximating that in the original plasma.

Blood derivatives mentioned in this discussion include Fractions I and V of human plasma prepared by methods described by Dr. E. J. Cohn and his associates.[11, 12] The major component of Fraction I is fibrinogen, the basic substance of the blood clot. Fibrinogen is a highly asymmetric protein that is relatively unstable, being incapable of withstanding exposure to temperatures sufficiently high for pasteurization but sufficiently stable to resist deterioration for as long as one year when stored in the dry state at refrigeration temperatures. A second clotting component, that is, antihemophilic globulin, is likewise contained in Fraction I. This factor has been identified as the inactive precursor of thromboplastin, being converted into the latter in the presence of material contained in platelets and in tissue cells.[13]

Fraction V, containing the albumins of plasma that are chiefly responsible for its osmotic activity, is available for therapeutic use, packaged as a 25 per cent protein solution in 5- and 25-gm. vials. Most stable of all plasma fractions, Fraction V tolerates pasteurization without loss of its original properties, a unique advantage as regards freedom from potential infectivity. When it is stored in solution at room temperature its stability is essentially unimpaired for at least five years. Considered from the therapeutic standpoint, a 5 per cent solution of albumin in isotonic saline causes an expansion of plasma volume after its intravenous injection that is equal to that produced by an equivalent injection of whole plasma, approximating 18 ml. per gm. of injected albumin.[14]

TRANSFUSION THERAPY IN SHOCK STATES

The role of blood-volume deficiency in the pathogenesis of shock due to hemorrhage, trauma and burn injuries and the transfusion requirements in such cases are sufficiently important to warrant de-

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tailed comment. The extent to which blood may be lost when hemorrhage is contained within a viscus or a muscle mass and the degree to which plasma may be depleted by leakage and red cells lost through hemolysis after a severe burn are frequently underestimated. Serious errors in clinical judgment and many therapeutic failures could easily be avoided by firm adherence to the concept that severe arterial hypotension following a traumatic injury or an event suggesting the possibility of a concealed hemorrhage, failing evidence of other causes, is indicative of severe blood loss and a blood-volume deficit exceeding 30 per cent, that is, 1500 ml. or more.[15] Conversely, it is important to recognize that patients with blood-volume deficits of 20 per cent or less are unlikely to exhibit marked hypotension as long as they remain in the horizontal position; and, by the same token, restorative transfusions sufficient to reduce a serious deficit to one of 20 per cent or less may succeed in returning the arterial pressure to normal or nearly normal levels after severe shock. A favorable therapeutic response at this stage is readily misinterpreted as an indication of adequate replacement, in which event transfusions may be interrupted prematurely, rendering the patient vulnerable to a recurrence of shock if hemorrhage is resumed. Shock is almost certain to reappear if such a patient is subjected to general anesthesia. Relapse may be provoked by unnecessary changes in the patient's position. In some cases its recurrence may be purely spontaneous, related to nothing other than the passage of time.

Patients in traumatic shock due to visible or concealed hemorrhage may be presumed to have lost proportionate amounts of red cells and plasma. Immediately after the injury the circulating plasma begins to expand, because of the withdrawal of fluid from the extravascular compartment. There is a corresponding drop in the hematocrit, indicative of erythrodilution, a consistent occurrence in patients who have lost a substantial volume of blood, unless they are severely dehydrated or develop an exudative infection, such as purulent peritonitis. The presence, degree and course of anemia in cases of shock therefore provide valuable confirmatory evidence concerning the magnitude of the blood loss.

Since ideal replacement therapy should supply all lost components in their original proportions, the transfusion of whole blood is clearly the treatment of choice in cases of shock due to hemorrhage or trauma. The most important requirement, however, is the maintenance of a blood volume adequate to support circulation, which can be accomplished very effectively, within certain limits, by the prompt injection of cell-free plasma, albumin solutions or a satisfactory plasma substitute, failing immediate access to whole blood. Despite the greater severity of anemia attending their use, no material risk is involved if red cells can be supplied soon enough to forestall the development of "irreversible shock." If red-cell concentrates were readily available for emergency replacement therapy, their effectiveness should prove to be greater, rather than less, than that of plasma or other cell-free materials in cases of this type. Transfusions of packed cells not only would elevate the blood oxygen capacity, which is obviously to be desired, but should also increase the blood viscosity. The peripheral resistance to blood flow should likewise increase, a change that might prove beneficial from the standpoint of relieving the arterial hypotension, that is, the shock state, as well as reducing the escape of blood from damaged vessels.

Burn Shock

The correction of blood loss is a primary consideration in the treatment of thermal burns.[16, 17] Two separate and distinct mechanisms, essentially unrelated except for their common origin, are responsible for the depletion of blood elements in these cases: the leakage of plasma through vessels that are damaged and abnormally permeable; and the lysis of red cells that have been exposed to excessive heat.[18] The hemolytic mechanism may involve a substantial proportion of the circulating red cells, those at the site of the burn being lysed immediately and others being eliminated in the course of a few hours or days, according to the extent of their injury. Red-cell destruction following severe burns, although extensive, is easily overlooked since it is masked by an even greater loss of plasma. Progressive erythroconcentration evidenced by a rising hematocrit, rather than erythrodilution and anemia, is the anticipated sequel to injury. Under these circumstances the evaluation of hematocrit changes is exceedingly difficult, and the latter are of relatively little value in controlling transfusion therapy. If treatment is guided solely by the course of venous hematocrit, on the assumption that the red-cell mass remains constant, it will fail to relieve the deficit of red cells. More importantly, the total blood volume will remain depleted, increasing the likelihood that irreversible shock or lower-nephron nephrosis may occur as a terminal complication.

Current concepts about the management of burn shock reflect an increasing dissatisfaction with plasma and a growing acceptance of whole blood as the restorative of choice, both in the early and in the late stages of burn treatment. Plasma transfusions are clearly indicated in the event that erythroconcentration progresses to an undesirable extent — that is, if the hematocrit level exceeds 65. No evidence of circulatory embarrassment has been observed in experimental subjects with red-cell concentrations increased to this range by repeated transfusions.[19] Whole plasma used in the treatment of burns should be free of incompatible isoantibodies, which promote even more hemolysis,[20, 21] aggravating the severity of anemia and favoring

the incidence of lower-nephron nephrosis. Human serum albumin, injected in 5 per cent solution, is precisely as effective as whole plasma as regards the expansion of plasma volume; because of its lack of isoagglutinins, its freedom from infective contaminants and its relative ease of administration, this material may be selected as the agent of choice. It must be emphasized that transfusion problems in burn cases, however complex, must not be allowed to obscure the importance of other therapeutic requirements, including the administration of appropriate electrolyte solutions for the correction of water, sodium and chloride deficits, which are commonly associated with this condition.

Nonoligemic Shock

Patients with severe arterial hypotension attributable to factors other than blood-volume deficiency, — for example, those with shock accompanying myocardial or pulmonary infarction, — occasionally must be considered from the standpoint of possible transfusion therapy. In no group of patients are the therapeutic indications for transfusion more difficult to evaluate, and in none is a correct evaluation more important in relation to prognosis. One of the primary problems is the establishing of an accurate diagnosis, for the presence or absence of a blood-volume deficit should obviously be determined before replacement therapy is begun. The most reliable basis for the detection or the exclusion of oligemia, failing a direct measurement of the circulating blood volume, is the presence, or progression, of anemia, accepting the latter as an index of erythrodilution. Diagnostic difficulties are compounded, however, in cases of nonoligemic shock complicated by anemia, especially if hemorrhage is a reasonable possibility, as in postoperative patients who develop myocardial infarction. Under these circumstances, a therapeutic trial of blood transfusion is scarcely open to criticism; however, when shock is clearly not due to blood loss transfusions are often withheld on the grounds that such treatment is futile and may be dangerous. The potential risks and benefits of blood transfusion in cases of myocardial infarction complicated by severe nonoligemic shock have been studied by Epstein and Relman,[22] who report that 30 patients receiving sizable injections of whole blood and plasma fared no less well, if no better, than did 20 comparable patients who received none. More than one third of the transfused group, moreover, exhibited favorable and sustained responses to transfusion. There was no apparent relation between the receipt of blood and the mortality, or the incidence of complications. The premise that transfusions are contraindicated in cases of this type could not be supported, whereas the cautious administration of whole blood, plasma or packed red cells seems entirely justified.

TRANSFUSIONS IN REFRACTORY AND HEMOLYTIC ANEMIAS

Patients with hypoplastic anemia that is unresponsive to hemopoietic stimulation of any type must depend for survival on the periodic injection of donor erythrocytes. Such therapy may be supplied effectively in the form of whole-blood or packed-cell transfusions. The latter, when available, are preferred in cases of this type, since the inclusion of plasma is not required, and its injection serves no useful purpose in recipients whose plasma volumes are already greater than normal. Since the volume of injected material is relatively small, red-cell transfusions are expeditiously administered in pairs. When paired transfusions are given, a thirty- to sixty-minute period should elapse between the injection of the first and second units — sufficient time for any pyrogenic reaction provoked by the first unit to occur before administration of the second unit is started. A reaction of this type usually has its onset between thirty and forty-five minutes after an injection of pyrogenic material is started. If a second transfusion were then in progress it would obviously have to be discontinued, and the remainder of the donor blood, being suspect, would almost certainly be discarded.

Two complications are likely to occur in patients with chronic anemia receiving repeated transfusions of whole blood or red cells over long periods of time: an increased susceptibility to pyrogenic reactions, for which no satisfactory explanation is available, and the development of hemosiderosis,[23] attributable to the deposition of excess iron derived from the donor erythrocytes. Although hemosiderosis is often regarded as a benign phenomenon, it has been held responsible by some observers for serious organic dysfunction. The progression of hemosiderosis to hemochromatosis, moreover, is by no means impossible, its development having been described in many patients who have received massive quantities of donor blood.[24] The existence of this potential threat warrants the curtailment of transfusion therapy to an acceptable minimum, no more blood being supplied to a patient than is required for symptomatic relief and for the maintenance of reasonable efficiency. Elevation of the blood hemoglobin concentration to a level of 12 gm. per 100 cc. may be deemed an adequate objective for any single course of transfusions in a patient with long-term requirements; a goal of 14 gm. per 100 cc., requiring from two to four additional transfusions and causing a correspondingly greater deposition of iron, is scarcely justified by any therapeutic advantages that might be associated with the higher hemoglobin concentration, such advantages being short-lived at best, and of debatable value.

Transfusions for complete correction of the red-cell deficit in patients with chronic uremia and anemia have been investigated from the standpoint

of their effect on renal function.[25] Although general clinical improvement has invariably occurred, in no case has efficiency been increased in response to therapy. The maintenance of a normal red-cell level in patients with cardiovascular disease, however, is of the utmost importance as regards their disability. The preoperative preparation of such patients and, indeed, of elderly patients in general, should include the complete correction of anemia by means of red-cell transfusions, the most effective measure available for the prevention of cardiovascular complications, to which these patients are unusually susceptible.[26]

Certain hemolytic disorders are characterized by the occurrence of "crises," which must be countered by emergency transfusions of whole blood or packed red cells. These include toxic anemias due to arsine, phenylhydrazine, hydroquinone and other hemolytic drugs; favism; and hemolytic jaundice of the acquired type. The transfusion requirements in such cases are frequently massive, equaling or exceeding those encountered in any other condition.[27] This is explained by the fact that the donor cells share the same fate as the patient's cells, being exposed to the same hemolytic mechanism and being eliminated with comparable speed. The situation in cases of hemolytic crisis is somewhat similar to that encountered in cases of active uncontrolled hemorrhage. In general, however, measures for the reduction of hemolysis are apt to be less effective than those available for the control of bleeding, the one outstanding exception being the treatment of acquired hemolytic jaundice with ACTH or cortisone.[28, 29]

Infants with erythroblastosis fetalis pose special problems in treatment, which are discussed elsewhere. In cases of toxic hemolytic anemia the only recourse is vigorous transfusion therapy, pending removal of the offending agent by some natural process of elimination. Patients with congenital hemolytic jaundice are unlikely to require transfusions except in preparation for splenectomy, a procedure that usually leads to a complete and permanent clinical remission. Generally speaking, transfusions in cases of congenital hemolytic jaundice are best withheld unless the anemia is of dangerous proportions, for although donor cells survive in normal fashion hemolysis of the patient's cells may be accelerated as a result of this therapy.[30] The spleen, the principal site of hemolysis, enlarges progressively as more and more of the patient's cells accumulate in its pulp, replaced by donor cells in the peripheral blood. The anemia of congenital hemolytic jaundice is difficult to eliminate by this means, and the technical problems attending the removal of an engorged spleen may actually be increased as a result of this preoperative preparation.

Patients with chronic hemolytic disorders for which no specific treatment is available, such as paroxysmal nocturnal hemoglobinuria, may require frequent transfusions for periods of many years. The complications attending therapy have been described in relation to chronic refractory anemia.

Transfusions in Hemorrhagic Disorders

The most important of the physiologic mechanisms responsible for the control of hemorrhage depends on the chemical conversion of *fibrinogen*, one of the soluble plasma constituents, into a hemostatic material called *fibrin*. Formed by the interlinkage of highly asymmetric fibrinogen molecules, fibrin is an insoluble protein with the characteristics of a linear polymer; its contribution to hemostasis is related to its fibrillar structure, its tendency to precipitate in the form of contractile bands or sheets and its capacity to jellify. By virtue of its fibrinogen content, blood is well equipped to repair its own channels, either by applying protective coatings or plugs at sites of vascular leakage or by sealing the entire lumen of a defective vessel with a clot.

Fibrinogen is converted to fibrin only under specific circumstances, normally so contrived as to ensure that clot formation can occur only in appropriate locations, only to an extent that is adequate and only when required. The agent directly responsible for the polymerization of fibrinogen is *thrombin*, which is formed by the activation of plasma *prothrombin*, its inert precursor. Prothrombin conversion, in turn, requires the presence of another plasma protein, *thromboplastin*, which is likewise inert until activated by a material contained in platelets and in tissue cells. Thromboplastin in the presence of ionized calcium permits the conversion of prothrombin to thrombin, and the quantity of thromboplastin that is available determines the amount of thrombin that is formed and hence the amount of clot produced. The speed of prothrombin conversion, an important factor in the determination of the effectiveness of a clot, is controlled by a protein catalyst that makes its first appearance when clotting begins and increases in amount as clotting progresses. According to Alexander,[31, 32] this catalyst, a soluble stable protein called "serum prothrombin conversion accelerator" ("SPCA"), is derived from an inert precursor that is activated in the presence of a labile protein[33] in plasma ("plasma AC globulin" of Ware and his co-workers,[34] "labile factor" of Quick,[35] "Factor V" of Owren[36] and "prothrombokinase" of Milstone[37]) and thrombin.

Essential participants in the clotting mechanism therefore include at least five soluble plasma proteins: fibrinogen; prothrombin, which, after activation, transforms fibrinogen into fibrin; a precursor of thromboplastin, that is, "thromboplastinogen," the prothrombin activator; a labile catalyst; and SPCA, the precursor of a stable accelerator (substances that speed the activation of prothrombin). These proteins, as well as calcium ions, are always in intimate contact in the plasma and are normally

present in abundant excess. One indispensable factor, however, is not dissolved in the plasma and is never present to excess, namely, the thromboplastin activator. This substance is locked within platelets and tissue cells — unavailable, therefore, until released from its intracellular position. Disintegration of these formed elements is consequently the trigger mechanism of blood clotting[38, 39] and the key to its control, since the occurrence, location and extent of platelet or tissue damage ultimately determine the occurrence, location and extent of fibrin formation. Platelets, which disintegrate at once when exposed to almost any surface other than normal intact endothelium,[40] are perfect vehicles for the storage and transport of this activator, for when intravascular clotting is desirable it is certain to be liberated at once and in the most strategic areas, whereas if the vasculature is normal this agent, though available, is powerless to function.

An abnormal bleeding tendency, except in patients with arterial hypertension and certain specific vascular disorders, is usually attributable to the lack of an essential clotting factor.[41] Deficiencies involving every individual component of the clotting mechanism except calcium have been discovered, each of these deficiency states having been responsible for a specific hemorrhagic disease (Table 7). *Hemophilia*, characterized by a lifelong tendency to bleed excessively and to produce destructive hematomas, is due to an inherited deficiency of the thromboplastin precursor.[42, 43] The hemorrhagic tendencies in patients with *thrombocytopenic purpura*, whose platelets are numerically deficient, and in those with *thrombasthenia*, whose platelets are defective, is based on the absence of thromboplastin activator,[44] which accounts for their petechial hemorrhages, spontaneous epistaxes, menorrhagia and general susceptibility to small-vessel bleeding. The basic defect in both groups of patients, that is, those lacking the activator of thromboplastin, is, of course, thromboplastin deficiency. The origin of the defect, however, differs in the two conditions, this difference perhaps explaining their clinical peculiarities. In hemophilia, for example, whereas both platelets and tissue cells provide ample quantities of thromboplastin activator, the supply of thromboplastinogen, the precursor, is too limited to permit extensive clotting, either inside or outside blood vessels; enough fibrin, however, is produced for the repair of minor vascular defects. In patients with platelet deficiency, on the other hand, intravascular fibrin formation is inadequate to prevent leakage from damaged blood vessels, but extravascular clotting, stimulated by tissue activator, can proceed in normal fashion. Hemorrhage therefore tends to be confined to the immediate vicinity of the leaking vessels, and circumscribed petechiae, rather than large hematomas, are formed.

Deficient or retarded thrombin activation and consequent clotting failure may be due to an insufficient quantity of thromboplastin inside a blood vessel, as in thrombocytopenic purpura, or outside, as in hemophilia. It has also been attributed in rare cases to the lack of the labile prothrombin accelerator factor, as in Owren's disease (parahemophilia),[45] and to the lack of SPCA.[46] Far more common, however, is lack of prothrombin itself due to inadequate absorption of its precursor, vitamin K[47]; or to a defect, congenital[48-50] or acquired,[51] of prothrombin production by the liver, occurring as one manifestation of liver failure or as the result of dicumarol inhibition. Marked hypoprothrombinemia, however caused, is responsible for a serious hemorrhagic diathesis characterized, like hemophilia, by purpura, ecchymoses and bleeding into any tissue or viscus. Finally, excessive bleeding has been caused by a decreased concentration of plasma fibrinogen. Fibrinogenopenia, due to a lack of production, may be acquired as a manifestation of severe liver damage.[52] Defibrination in vivo, occurring as a result of extensive clotting or possibly due to increased fibrinolytic activity in the blood,[53] has been described as an uncommon complication of traumatic shock[54] but a relatively frequent accompaniment of severe placental separation[55] and of intrauterine death.[56] Afibrinogenemia, that is, the complete absence of fibrinogen, is included among the rare congenital anomalies.

Hemophilia

Bleeding from small superficial vessels in patients with hemophilia can usually be checked by the local application of cold pressure dressings and the use of hemostatic preparations containing thrombin, that is, powdered thrombin or gelatin foam saturated with thrombin solution,[57] the objectives being to promote vasoconstriction and to produce clotting at the site of hemorrhage. Thrombin prepared from human blood and thrombin of animal origin are equally effective as clotting agents; the latter, however, can be employed without danger from the standpoint of transmitting virus hepatitis, whereas this risk attends the injection of any product derived from pooled human blood, particularly if, like thrombin, it is so labile that it cannot be sterilized by any method ensuring effective virus decontamination and cannot be preserved except in the dried or frozen state, that is, under conditions that are optimal for the preservation of viruses. The effectiveness of local hemostasis in cases of hemophilia depends as much on the degree of vasoconstriction produced by cold and pressure as on the clotting effect of thrombin, for clots so produced are situated entirely outside the injured vessels, scarcely a strategic location for the sealing of vascular leakage.

The basic defect in hemophilia can be repaired and the hemorrhagic tendency eliminated com-

pletely, if only temporarily, by the injection of thromboplastinogen, which may be given in the form of fresh whole blood, whole plasma or Plasma Fraction I.[58-60] In view of the relative instability of the antihemophilic globulin, effective therapy requires the use of blood collected within a period of twenty-four hours or less, or of plasma that has either been removed from fresh blood immediately before use or preserved in the dry or frozen state since the day of its separation from fresh donor blood. Plasma injections of 100-250 ml. usually suffice to reduce the clotting time to within the normal range of six to twelve hours, after which it may increase to its original level in the course of the ensuing six to twelve hours. As emphasized by Quick,[57] however, the clotting time is a relatively poor criterion of therapeutic needs or responses in this disease, a far more reliable basis for their evaluation being the prothrombin consumption, which should be measured routinely in every case. Whether transfusions are given to halt active hemorrhage or are provided as a prophylactic measure in preparation for operation, treatment should entail the injection of at least 1000 ml. of fresh whole blood, 500 ml. of plasma or a corresponding amount of antihemophilic globulin concentrated from normal human plasma, subsequent treatment being regulated on the basis of the changes in prothrombin consumption noted in response to the initial injection. Periodic injections of active material given at weekly intervals, or oftener, afford a certain measure of protection against recurrent hemorrhage, this prophylactic device having reduced the frequency and severity of bleeding episodes in many cases of hemophilia.[61]

Thrombocytopenic Purpura

Of all bleeders, patients with platelet deficiency are among the most numerous, the most seriously affected and the least amenable to replacement therapy. Those with "idiopathic thrombocytopenic purpura" are often improved, and occasionally cured, by splenectomy. Some, whose disorder is apparently attributable to the rapid destruction of platelets by an "autoantibody," that is, by a mechanism analogous to that in "acquired" hemolytic jaundice, which may develop concomitantly,[62] have been observed to respond favorably to the administration of ACTH or cortisone.[29, 63] When thrombocytopenia occurs as a manifestation of bone-marrow failure, caused, for example, by toxic depressants, ionizing radiation or neoplastic invasion of the bone marrow, replacement therapy offers the only logical hope of success. Unfortunately, because of their extraordinary lability, platelets are notoriously difficult to preserve in vitro. These cells agglutinate promptly on contact with air interfaces and with foreign surfaces of all types, unless the latter are altered by the application of a so-called "non-wetting" or "platelet-repellent" surface. Successful transference of platelets from one person to another has been achieved, so far as we are aware, only by means of direct transfusions performed with equipment constructed entirely of plastic or coated material.

The survival period of platelets may be as brief as two days, based on animal experiments of Lawrence and Valentine,[64] or it may be as long as eight days, judging from the duration of thrombocytosis after injections of human blood, as reported by Hirsch and Gardner.[65] The anticipated response

TABLE 7. *Differential Diagnosis of Clotting Disorders.**

DISEASE	DEFICIENCY	CAPILLARY BLEEDING TIME	CLOTTING TIME	CLOT RETRACTION	PROTHROMBIN ACTIVITY	PROTHROMBIN CONSUMPTION	PLATELET COUNT	CAPILLARY FRACILITY
Hemophilia	Thromboplastin precursor	Normal	Prolonged	—	Normal	Reduced	Normal	Normal
Thrombocytopenic purpura, idiopathic or secondary	Thromboplastin activator	Prolonged	Normal	Reduced	Normal	Reduced	Reduced	Increased
"Thrombasthenia" (pseudohemophilia; hereditary hemorrhage diathesis)	Thromboplastin activator	†	†	Reduced	Normal	Reduced	Normal	Increased
Hypoprothrombinemia	Prothrombin	‡	‡	Normal	Reduced	Normal	Normal	‡
SPCA deficiency or labile-factor deficiency (Owren's disease, essential hypoprothrombinemia; parahemophilia)	Prothrombin activator	Normal	Prolonged	Normal	§	Reduced	Normal	Normal
Fibrinogenopenia; afibrinogenemia	Fibrinogen	Normal	¶	¶	Normal**	Normal	Normal	Normal

*Condensation of material tabulated on pages 220-224 in "A Syllabus of Laboratory Examinations in Clinical Diagnosis," edited by T. H. Ham, published by Harvard University Press, Cambridge, 1950.

†Occasionally normal, occasionally prolonged.

‡Increased in severe cases only.

§Prothrombin clotting time prolonged when one-stage method is used, but normal when tested by plasma-dilution technic.

¶Clotting absent if fibrinogen concentration is reduced below 50-75 mg. per 100 cc.

**Addition of fibrinogen is required for test, which then indicates normal prothrombin activity.

to platelet injections, though brief, cannot be dismissed as therapeutically valueless on that account, for in many cases thrombocytopenia itself, though dangerously severe, is likewise brief. With respect to the potential effectiveness of platelet transfusions, Hirsch and Gardner's patients, who received platelet-rich blood from polycythemic donors, were relieved of their hemorrhagic tendencies when their platelet counts had risen to approximately 100,000 per cu. mm., at which level their bleeding time, capillary fragility and prothrombin conversion reverted toward normal. With further improvements in the collection and processing of donor blood, it is reasonable to predict that injectable suspensions of intact, viable platelets will some day be available for the treatment of abnormal bleeding due to thrombocytopenic purpura and thrombasthenia.

Prothrombin Deficiency

The value of blood transfusions in the treatment of hypoprothrombinemia is well established. Restoration of the prothrombin concentration to but one tenth of its normal level is usually sufficient to eliminate abnormal bleeding. By the same token, normal donor blood contains prothrombin in such ample excess that relatively small quantities are required for therapeutic effect. Hypoprothrombinemia may or may not be accompanied by the lack of an accelerator factor. Rarely, cases of abnormal bleeding have been due solely to a deficiency of the labile plasma component or of SPCA.[45, 46, 66]

A deficiency of prothrombin can be corrected by injections of fresh or stored plasma; SPCA deficiency responds to fresh or stored serum, as well as to plasma. Labile factor, on the other hand, can only be furnished by injection of fresh plasma, for it is consumed almost completely in the process of clotting, the remainder disappearing altogether within one or two days after collection.

Fresh plasma is capable of restoring any component of the prothrombin complex. For that reason it is often selected as the agent of choice in treating hypoprothrombinemia, although the majority of cases are fully as responsive to stored plasma. The relative merits of plasma as compared to serum and those of stored versus fresh material, as well as the dosage requirement, may be predicted in individual cases by observing the effect of these materials in vitro on the prothrombin-clotting time and the prothrombin consumption prior to treatment. One to two hundred ml. of plasma or double this volume of whole blood will usually suffice to assure hemostasis temporarily, most patients requiring repeated injections at intervals of twenty-four to forty-eight hours until the basic cause of the hypoprothrombinemia has been eliminated.

Fibrinogen Deficiency

Rare circumstances in which plasma fibrinogen may be lacking include the occurrence of massive hemorrhage, severe traumatic injury and extensive thermal burns; the development of advanced liver disease; and the existence of a rare congenital defect denoted by the absence of fibrinogen formation. Far more important as causes of afibrinogenemia, however, are two obstetrical complications: toxic separation of the placenta and intrauterine death.

Dieckmann[67] in 1936 reported the finding of a low concentration of fibrinogen in the plasma associated with defective clotting and abnormal bleeding in 5 out of 11 cases of *abruptio placentae*, all of these abnormalities disappearing post partum. Weiner, Reid and Roby,[55, 56] who have completed a systematic and thorough investigation of the clotting mechanism in 70 patients with moderately severe or severe placental separation, have described the development, under observation, of serious fibrinogen deficiency in approximately 30 per cent of the latter, as well as in 3 of 15 cases of intrauterine death caused by Rh isoimmunization. Confirmatory findings in one case of afibrinogenemia complicating premature separation of the placenta have also been reported by Moloney.[68]

Dieckmann ascribed the afibrinogenemia of his patients to an exhaustion of plasma fibrinogen by massive hemorrhage and clotting at the placental site. A different explanation for its occurrence in these patients, and also in other types of cases, is based on the concept that clots may form and again disappear, or that clotting may be prevented altogether, because of the activity of a so-called "fibrinolysin"[52, 54] (which, one must infer, is also a "fibrinogenolysin"). This concept is not, however, immune to challenge. Moreover, as pointed out by Weiner and Reid,[69] all the pertinent observations that have been reported in connection with these cases are explainable on the grounds of in-vivo defibrination of the circulating blood. Intravascular clotting, with formation of capillary thrombi, might well follow the introduction of material with active thromboplastin activity, such as amniotic fluid,[70] into the maternal bloodstream at the site of placental separation, with results that are closely comparable to those observed in experimental animals subjected to similar infusions.[70-72] Completely defibrinated blood contains no fibrinogen and cannot, of course, be clotted. Partially defibrinated blood, containing fibrinogen in low concentration, may form clots that are small, friable and too unstable to maintain their own integrity, even in the complete absence of a "lysin."

In any event, whether fibrinogen is destroyed in these patients by a fibrinolytic enzyme or is lost in the form of fibrin precipitates, it is vitally important that it be replaced, and maintained at a safe level (that is, exceeding 100 mg. per 100 cc.),

pending the evacuation or removal of the uterus, at which time spontaneous recovery may be anticipated. The only feasible method of accomplishing this replacement is by the administration of Fraction I, approximately 30 to 50 per cent of which by weight, is fibrinogen; 4 to 6 gm. of this material, injected intravenously, provides adequate hemostasis.

Speed and accuracy of diagnosis is of paramount importance in the prevention of death in cases of afibrinogenemia. If suspected, the clotting defect is readily identified or its presence excluded by observing the clotting of fresh unmodified venous blood, — inadequate clotting or absence of clotting being an indication of dangerous fibrinogen depletion.

Other Clinical Uses of Blood and Blood Derivatives

Parenteral Nutrition

Complete nitrogen balance can be achieved and maintained by intravenous injections of whole plasma or of serum albumin as the sole source of exogenous protein. These materials would serve admirably as nutrients except for their colloid osmotic activity, the latter causing an undesirable expansion of the recipient's plasma volume while delaying their own utilization in the metabolic pool.[73] Their hypervolemic effects, in particular, preclude the long-term use of these agents for nutritional purposes.

Whole blood, though containing four times as much utilizable protein as plasma or isotonic albumin solutions, is even less valuable as a nutritional source. Expansion of the patient's blood volume by the cellular fraction is greater and more prolonged than that produced by the soluble proteins. Moreover, the utilization of the intracellular protein, representing three fourths of its total contribution, is incomparably slower, only about 1 per cent of this material becoming available for utilization each day. The most important barrier to its use, however, is the inevitable production of hyperferremia, which, if excessive, creates an unnecessary risk from the standpoint of possible hemochromatosis.[24]

Preferable, theoretically, as a protein nutrient, and currently the most promising agent for the restoration of nitrogen balance in cases of hypoproteinemia, is globin,[74] ample quantities of which could be made available as a by-product of blood fractionation. This material is utilized efficiently, maintaining nitrogen balance without supplementation when injected daily in 60-gm. doses, that is, 1000 ml. of a 6 per cent globin solution.[75] The globin molecule (half-moiety) is smaller than that of albumin, consequently the former escapes more readily into the urine. By the same token, however, globin diffuses more rapidly into the extracellular compartment and therefore is promptly available for utilization. As regards the problem of diet selection in general, it may be observed that the use of a whole protein in contrast to a protein hydrolysate is rarely indicated in parenteral feedings. Although similar in nutritional value to corresponding quantities of blood protein, hydrolysates can be employed with greater safety and at far less expense.

Control of Edema and Ascites

The distribution of water between the circulating blood and the extravascular fluids is influenced to a great extent by the amount of albumin in the plasma.

When the latter is reduced, water tends to escape from the blood and migrate into the extracellular-fluid compartment. In response to the ensuing anhydremia the kidneys then proceed to retain water, as though responding to general dehydration, with the result that the total body water is abnormally increased in amount. Except in patients with portal hypertension, the bulk of this excess accumulates in the extracellular-fluid compartment, causing edema; the remainder diffuses into the serous cavities, the blood volume remaining approximately normal. If there is a coexisting portal hypertension, the preponderance of the accumulation is directed into the peritoneal cavity because of the increased hydrostatic pressure in the splanchnic capillaries; that is, the patient develops ascites. Essential for the restoration of a normal distribution of body water in either case is the restoration to normal of the plasma albumin concentration. As one means to this end, intravenous injections of salt-poor human serum albumin have been supplied in a variety of hypoproteinemic states, especial benefit having been reported in certain patients with hepatic cirrhosis and ascites, the nephrotic syndrome, idiopathic hypoproteinemia and edema of malnutrition.[76]

The arrest of ascites, often a prerequisite to successful dietotherapy, may be accomplished in some, but not all, cases of cirrhosis[76, 77] by giving salt-poor albumin in sufficient quantities to maintain an effective osmotic gradient between the plasma and the ascitic fluid.[76] The abdominal cavity having been tapped as dry as possible by abdominal paracentesis, albumin therapy is begun, 50 to 100 gm. of this protein being injected each day until ascitic fluid ceases to accumulate, — usually a matter of about two weeks. Reaccumulation of fluid thereafter can often be avoided by 20- to 100-gm. doses of albumin injected weekly or biweekly pending the spontaneous recovery of normal protein production by the patient.

The use of albumin in patients with the nephrotic syndrome is often of great value.[78, 79] Repeated injection of concentrated, salt-poor solutions of this material, given in 50-gm. doses, provokes a satisfactory diuresis in approximately one half of the cases so treated. The character of this response is visualized as follows[78]: Immediately after each in-

jection of albumin, extracellular fluid enters the vascular compartment, diluting the blood until the concentration of plasma proteins has been reduced nearly to its original level. Concomitantly, as the blood volume expands, an increased volume of fluid filters through the renal glomeruli and is excreted. While this filtrate is in transit through the tubules, however, its sodium is extracted and is returned to the circulating blood. The concentration of plasma sodium is therefore increased, the peak of this elevation occurring sixty to ninety minutes after the injection. At this point, if glomerular filtration is adequate and tubular flow sufficiently rapid, some sodium may escape reabsorption. If a substantial amount of sodium does escape in the urine diuresis will be effective and will be followed by a sustained increase in the plasma protein concentration. If little or no sodium is lost its concentration in the plasma continues to be elevated; as a result, diuresis is halted and, despite further albumin injections, the urine output remains reduced.

It must be emphasized that the use of albumin, as long as its present scarcity continues, is justified only when the therapeutic indications are compelling and precise, as in preoperative cases with severe protein deficiency and in cases of pre-eclamptic toxemia or of nephrosis complicated by infection. In general, patients with hypoproteinemia whose disorder, irrespective of type, is chronic, static and devoid of immediate danger are not suitable candidates for a long-term intensive albumin regimen, any benefits accruing in such cases being relatively unsubstantial, and entirely outweighed by the risks and wastage entailed.

Passive Immunization

Blood transfusions for the transfer of specific immune antibodies from convalescent donors to susceptible contacts have been employed effectively in controlling the spread of many epidemic infections, including measles, mumps and yellow fever. Immune transfusions have also been of value in treating certain infections, notably herpes ophthalmia and scarlet fever. Recently, with the advent of Plasma Fraction II (the gamma-globulin fraction) into the practice of preventive medicine, accomplished in 1941 through the technical achievements of Dr. E. J. Cohn and his colleagues,[11] together with the facilities of the National Red Cross Blood Program, the importance of prophylactic transfusions has vastly increased.

Clinical applications of gamma-globulin therapy are completely described elsewhere[80, 81] and are appropriately omitted from the present discussion. It is pertinent to observe, however, that the ultimate importance of this plasma fraction is inadequately appreciated, for its useful potentialities in clinical practice and in public-health medicine have scarcely begun to be exploited. The sole source of the gamma globulin, thus far, has been blood from unselected donors who have been secured without reference to their immune status. The effectiveness of this agent in measles prophylaxis and in the prevention of infectious hepatitis therefore merely reflects the prevalence of immunity for measles and hepatitis virus existing in the general population, that is, the endemic character of those infections.

Fraction II contains, in a 25-fold concentration, all the immune antibodies that were present in its parent plasma. Were this plasma to be prepared by pooling bloods obtained from selected donor panels, comprised exclusively of convalescent and hyperimmune persons with antibodies of particular specificity, the clinical value of its gamma-globulin fraction would be enormously enhanced. Access to ample quantities of hyperimmune gamma globulins of certain varieties could lead to many important advances in infectious-disease therapy. Whether or not donors, selected on this basis, will even become available in the necessary number for such a prospect to materialize depends on the growth and development of a national blood program, its future conduct and its future support, in times of peace as well as of war.

Transfusion Reactions

Transfusion reactions have increased somewhat in the past ten years because of the increased use of blood, but have decreased considerably in proportion to the number of transfusions given. The first step in their control has been a clearer description of their distinguishing characteristics so that their classification could be made on a rational basis; the second has been the dissemination of knowledge of their diagnostic features; the third has been a definite program of treatment; and the fourth, a systematic plan for their prevention or the diminution of their effects. Considered in the order of their clinical importance, they are now classified as hemolytic, febrile (or pyrogenic), infectious, anaphylactic, transfusion jaundice, "speed reactions" and gas embolism.

Although the hemolytic group of reactions covers several types, our primary concern remains with hemolysis that follows the agglutination of the donor's cells by the serum of the recipient in the case of a mismatching under the ABO or Rh systems. Experience has shown that equally disastrous results can follow the destruction of the cells of the recipient after the infusion of universal donor blood in which the plasma has a high titer of agglutinins for the recipient's cells. Destruction of the donor's cells by improper storage and handling, with liberation of hemoglobin, is a frequently unrecognized source of trouble for the recipient. More obscure sources of difficulty are cold agglutinins and isoimmunization to blood-group factors other than A, B or Rh on the part of the recipient.

The symptoms of hemolytic reactions are as characteristic now as they were in the early part of the century; burning in the vein above the transfusion needle, precordial and lumbar pain, nausea, vomiting, tachycardia, hypotension and flushing are characteristic. Chills and fever may occur in these reactions as they do in others. Any or all of these symptoms may be absent. Under anesthesia the recognition of such a reaction may be impossible, but an observer should be suspicious if a patient has an increased pulse rate, a fall in blood pressure and flushing unaccounted for by the activities of the surgeon. These signs may be entirely absent, however. The diagnosis may be suggested by the clinical signs and symptoms but is made by the immediate detection of free hemoglobin in the serum of the recipient. A definite pinkish color will be present for three to four hours after discontinuance of an incompatible transfusion. After this time a search should be made in the patient's urine, if he has formed any since transfusion, for free hemoglobin. A simplified method for the detection of free hemoglobin in the blood serum is to withdraw venous blood, after application of a tourniquet, through a dry needle into a dry test tube without the use of the negative pressure introduced by a syringe. This blood should then be spun down in a centrifuge. Another method that avoids clot formation is the withdrawal of blood by means of a needle and a syringe that have been moistened with saline solution. This blood is then mixed with citrate and spun down. A pinkish color in the serum is diagnostic of a hemolytic reaction; its absence, if the blood is drawn within three hours of the reaction, is evidence that hemolysis is absent or, if present, of so small a degree as not to be clinically significant.

The first treatment of a patient with a suspected reaction is to discontinue the transfusion. Shock, if present, should be treated according to the classical rules for shock treatment. Compatible whole blood (if indicated) may be given after the source of the reaction has been investigated, as outlined below. Subsequent treatment depends on the degree of oliguria present. Urine of high specific gravity excreted into the bladder after transfusion points to no interference with kidney function, and thus no treatment would be necessary. Relative degrees of kidney shutdown are best controlled by careful attention to fluid and electrolyte balance. Attempts to alkalize the urine may produce alkalosis in the presence of anuria and are seldom helpful in promoting urinary excretion. When acidosis is present it should be treated by administration of soda bicarbonate by mouth or rectum or of sodium racemic lactate by vein, care being taken to keep the blood sodium at a normal level. Diuretics are dangerous to the kidney in failure and cannot be expected to stimulate diuresis. During the oliguric period the fluid intake should be limited to the estimated insensible fluid loss plus a volume equal to the urinary output. Stripping of the kidney capsule, high spinal anesthesia and sympathetic blocks have their advocates but are usually dangerous to patients in this condition and are rarely, if ever, beneficial. If persistent urinary retention becomes hazardous after a period of days, clearing of the blood stream may be effected by peritoneal lavage[82-84] or use of the artificial kidney.[85] The latter has come to be considered the safer and more effective of the two methods; it is available in most large medical centers, to which patients can be brought from the most remote communities in a few hours by air. A more costly method is that of exchange transfusion.[86]

Advances in the prevention of hemolytic reactions have been important in the last ten years. The most fundamental of these has been the taking over of the control of blood banks by physicians or trained doctors of science who have the knowledge of laboratory technics, the interest and the time to devote to the work. Under their guidance technicians have been trained specifically for blood-bank laboratories to replace interns, nurses and others who did this work as a part-time job with a background of little or no special training. Along with an improvement in the training of personnel have come not only new and better serums and technics but the setting up of more careful systems of performing large numbers of groupings and cross-matchings with safety. The recognition of clerical or mechanical errors as a serious hazard has led to an improvement in the labeling of test tubes, better records and careful checking of results. The system of doubly checking all laboratory work from start to finish by separate persons is not new but owes much of its widespread adoption to the impetus given it by its successful if somewhat elaborate use in the Mediterranean Theatre in World War II, and its adoption by the Massachusetts State Blood Program after the war. It is now used widely by many large banks but is not as necessary for small ones, in which the small volume of work is less conducive to clerical errors. A further lessening of transfusion dangers has come from a better system of handling the blood after it has left the blood bank. Many hospitals insist that the person who is to administer the transfusion to the patient must personally bring the flask from the bank to the bedside. Others, relying on nurses or physicians trained in intravenous technic, require that these workers check on all details of identification of both the patient and the blood to be given before starting the transfusion. The wisdom of having a person familiar with the signs of a hemolytic reaction remain at the patient's bedside for at least five minutes after an infusion of blood has been started has been recognized for many years, as in that period the symptoms of nearly all fatal hemolytic reactions become manifest. The insistence on this

one principle alone has done more than any other single measure toward preventing deaths from following undetected laboratory errors. The last but not the least important step in preventing these reactions has been the investigation of each one that has occurred, followed by the correction of the source of error and a discussion of the occurrence with hospital personnel and directors of other banks so that similar episodes might be prevented.

The system of investigation of hemolytic reactions is now well enough standardized that it can be taught as a routine to all physicians who are responsible for transfusing patients. The transfusion flask should be returned to the bank after such a reaction, even though it contains but a few drops of blood. The group and Rh factor can then be determined on the blood actually run into the patient and not merely on the pilot tube that accompanied it. A fresh sample of blood should then be drawn from the patient for regrouping, Rh typing and cross-matching. If no error is detected by this method, partial destruction of the red cells in vitro prior to transfusion, or the presence of unusual agglutinins in the patient's blood, should be suspected. Experience has shown that considerable hemolysis can take place in a flask of sedimented banked blood, without appreciable color change in the supernatant plasma, so that casual observation may not detect the presence of a dangerous amount of free hemoglobin.[87] Resuspension and resettling are necessary to show the color change. The suspicion of such hemolysis should lead to a thorough investigation of the entire handling of the blood from donor to recipient. The detection and identification of rare agglutinins should be investigated by means of the Coombs test.

The febrile (or pyrogenic) reactions are less complex than the hemolytic. They are seldom dangerous, though often terrifying. They are characterized by fever and chills of varying degrees of severity appearing during or shortly after transfusion. Much has been written about them, but to date their causes often remain difficult to detect because so many factors can be involved. First there are pyrogens (breakdown products of bacterial metabolism), which are resistant to ordinary heat sterilization. They are found in water, tubing, bottles and so forth, where bacteria have been active. Secondly, there are dead bacteria that have not been removed prior to sterilization. Thirdly, there are various chemical substances in tubing or glassware that have not been removed by the cleansing and rinsing process. Fourthly, there are particles of old blood adherent to glass, tubing or needles that have been used previously and improperly cleaned. Fifthly, there are certain disease states in which a patient will have febrile reactions after nearly every transfusion. This introduces a sixth factor that as yet defies analysis, although some observers think that certain disease states cause a hypersensitivity to pyrogens. It must be stressed that in some instances a slight febrile response to transfusion may be the only evidence of a hemolytic reaction, which would not be discovered unless the blood of the recipient were thoroughly investigated. The term "pyrogenic reaction" is a misnomer; "febrile" is nonspecific, as other types of transfusion reactions are accompanied by fever. No really good name has been applied to this group.

The diagnosis of this type of reaction is made on a basis of the clinical signs in the absence of hemolysis, infection or other cause for fever. The treatment is to discontinue the transfusion and to make the patient comfortable. Prevention largely consists in constant surveillance over the methods of preparation of tubing, donor flasks and blood preservatives. Most banks using disposable equipment can report reactions to the manufacturers; those having reusable tubing and flasks must frequently check on the preparation of all articles, particularly rubber tubing, as the crevices of old rubber will frequently harbor particles of blood. Prophylaxis is, of course, only applicable to those patients whose diseases have made them prone to such reactions. After checking the donor-recipient compatibility by the Coombs method to eliminate a possible hemolytic reaction in a person who may have been previously sensitized, the use of antipyretics is advisable before transfusions. Antihistaminics have not been effective. Experience has shown that the salicylates have been most valuable. The most effective method is to give 1.0 gm. of acetylsalicylic acid once an hour for two hours before transfusion and again at the time of actual infusion. This will frequently reduce the severity of the reaction, eliminate it entirely or postpone its occurrence until after all the blood has run in. Washed red cells may be effective in preventing these reactions when they are caused by substances in the plasma to which the recipient is sensitive, as suggested by Dameshek.[88]

Infectious reactions are the result of the administration of blood heavily laden with dead or viable bacteria. Although it is not always recognized that properly refrigerated banked blood can act as a culture medium, there are many organisms, particularly those that are normal residents of the skin, that not only can exist but also can propagate at low temperatures. Usually these organisms are alive at the time of transfusion but occasionally will have died after having multiplied enormously. In this regard it is necessary to both smear and culture the blood that has caused the reaction. The symptoms are those of a febrile reaction, as outlined above, with signs of shock and an overwhelming septicemia. The diagnosis can be made on observation but must be confirmed by examining the blood from the donor bottle as well as performing a blood culture and smear on the recipient. The treatment is to discontinue the transfusion promptly

and to administer intravenously aureomycin or other antibiotics that have a wide spectrum of bactericidal efficiency. Death usually results within a few hours or from one to two days after transfusion. Recovery, when it occurs, is slow, with a gradual lysis of the fever over a period of days.

Because of the high mortality associated with these reactions no effort should be spared in tracking down the cause of contamination. The commonest factors are the improper sterilization of the needle, tubing or donor flask and its content and improper preparation of the donor's skin. Contamination of the apparatus by the fingers of the phlebotomist and introduction of room air into the transfusion flask at the time of phlebotomy or by means of an improperly sealed bottle are other sources of bacterial ingress. The growth of bacteria in stored blood is much limited by refrigeration, as a rule; hence, it is important to refrigerate blood from the moment when it is drawn until it is infused. Breaks in the aseptic technic of phlebotomy are far from rare.

Anaphylactic or allergic reactions are the results of the patient's sensitivity to a foreign protein in the plasma of the donor or, in some instances, to the transfer of antibodies from a sensitized donor with consequent temporary transfer of an allergic state to the recipient. These reactions are usually manifested by urticaria, rashes of various sorts or hives, during or shortly after a transfusion of blood or plasma. Occasionally swelling of the face and joints will appear. Rarely, a reaction similar to that caused by a sensitivity to horse serum will occur, with rales, asthmatic wheezes, severe dyspnea and even death. Three such severe reactions have occurred in 75,000 transfusions carried out at the Massachusetts General Hospital, all of which were relieved by the prompt administration of adrenalin. Some patients, particularly those who have a wide range of allergies, will have a mild anaphylactic reaction whenever transfused.

The treatment is to discontinue the transfusion. Antihistaminics are helpful; adrenalin given intravenously in small doses is rarely necessary. As their occurrence is infrequent (0.5 per cent in our series), prophylaxis is unnecessary as a routine. For persons who have had one or more mild reactions previously, the use of an antihistaminic drug administered an hour before a transfusion will usually abort them. The use of washed red cells is effective in preventing them, as it eliminates nearly all the plasma. Adrenalin should be available, and the patient should be watched closely during infusion if he is known to have had such a reaction before.

"Transfusion jaundice" refers to a heterogeneous group of reactions characterized by nonobstructive jaundice. This group can be divided into two general categories — hemolytic and infectious. The first of these covers the hemolytic jaundice resulting from a prolonged breakdown of donor cells in the circulation of the recipient after transfusion. It can arise from the cells' being very fragile as a result of prolonged or improper storage or from their gradual agglutination and destruction by agglutinins in the serum of the recipient or from gradual destruction of cells of the recipient by agglutinins in the serum of the donor. The classical signs of a hemolytic reaction, such as shock and renal failure, are usually absent. Usually the treatment is expectant; replacement transfusion therapy is rarely necessary as long as kidney function is unimpaired. An effort should be made, however, to ascertain the cause of the jaundice. The blood of the donor and the recipient should be studied, as after a hemolytic reaction, for sources of incompatibility, particularly in the A and AB subgroups, Rh system and for other known factors. The use of the Coombs test should always be included in these studies. If no incompatibility can be found, the handling and storage of the blood should be investigated and appropriate remedial measures taken to prevent undue fragility of the donor's cells in subsequent transfusions, if such was the established cause for this reaction.

Infectious jaundice is caused by a virus present in the serum of the donor that is passed on to the recipient by infusion. The early form occurs anywhere from a few hours after a transfusion up to a period of several weeks later; it is accompanied by fever and signs of hepatitis. The later form is more insidious in onset, and fever, if present, usually disappears rapidly. It is followed by a prolonged afebrile jaundice. The onset may take place anywhere from a month to six months after inoculation with the virus. This type is currently referred to as "homologous serum jaundice." Neither type confers immunity to the other. In some instances the donor has been found subsequently to have developed jaundice; hence he was presumably in the incubation period of the disease at the time of donation. Investigation as to the source of the jaundice is complicated by the fact that a patient may have been inoculated with the virus, — not by his transfusion but by means of needles or other instruments previously used on an infected patient and not properly sterilized afterward.

The treatment is that of any hepatitis or infectious jaundice. The prognosis is usually favorable, but a considerable mortality is sometimes reported. The prevention of these reactions lies in the careful screening of donors for a history of recent jaundice or hepatitis or in looking for the signs of such. Some banks conduct chemical tests for jaundice on the serum of all donors in an effort to reduce the number of such reactions. These tests will eliminate donors suffering from obstructive or hemolytic jaundice of a nature unharmful to the recipient; they fail to detect hepatitis in the pre-jaundice or carrier stage but are nevertheless useful. Until such time as an accurate test has been developed

to detect an infectious virus present in the donor's serum, we shall have no adequate method of preventing these complications of transfusion. The present trend is to regard persons who have had infectious hepatitis with or without jaundice as possessing immune bodies of value to potential recipients if they are used six or more months after recovery from the disease. This trend is based on the findings of Stokes and others that cases of homologous serum jaundice are rarely if ever traced to a donor who had had jaundice but in some instances have been traced to persons who have repeatedly caused serum hepatitis in patients through blood donation without any manifestations of the disease themselves.[89] The incidence of homologous serum jaundice following the use of plasma has been materially lessened but unfortunately not eliminated by the use of ultraviolet-light irradiation.[90] For hospitals making their own plasma the avoidance of any but small pools or the making of plasma in individual units from one or more donations of blood has greatly cut down the potential spread of the disease from one donor to many recipients. The necessity of identifying the blood groups and Rh factor of plasma made from one or more donations and giving it to patients of the same type is obvious. Exceptions can only be made safely by the addition of Whitebsky's A- and B-specific substances immediately prior to infusion, if it has been determined that immune anti-A or anti-B antibodies are not present.[91, 92] A low titer of anti-A or anti-B in the plasma (less than 100) will eliminate the necessity of using specific substances if no hyperimmune A or B is present. Any human blood derivative (such as thrombin) is a potential source of infection with the virus.

The so-called "speed reactions" are not true reactions in the sense of the others previously described. They are actually due to circulatory overloading, resulting in right-sided heart failure. They may be caused by over-rapid infusion or improper selection of material for intravenous use or both. They are manifested by increased venous pressure and pulmonary edema and usually result in death. The signs of heart failure may occur during infusion or even some hours afterward. The responsibility for avoiding them lies with the physician attending the patient and the person administering the fluid. If care is exercised in the intravenous administration of fluids these reactions can be completely eliminated. The treatment is the discontinuance of the infusion and immediate institution of suitable therapy for heart failure. Their prevention is relatively simple if the following precautions are followed: first, slow administration of blood or other fluids intravenously (at 40 drops per minute or less) in anyone who is old or who gives evidence of a diminished cardiovascular reserve; secondly, careful selection of the therapeutic agent to be administered (it is generally agreed that patients on the edge of or in failure, in uremia or suffering from a profound anemia [5 gm. of hemoglobin per 100 cc. or less] should receive packed red cells rather than whole blood in the treatment of their anemia); thirdly, materials such as serum albumin, in which the molecule is small and hence cause a considerable withdrawal of fluid from the tissues into the circulation, should be used with extreme caution or in a dilute form. It must be clearly stated, however, that in replacing blood being lost by hemorrhage, rapid infusion to keep up with blood loss will rarely if ever cause heart failure.

Gas embolism arises from the unfortunate introduction of air, oxygen or other gases into the venous system at the end of a transfusion in which a gas has been employed to produce pressure in the transfusion flask. Gas embolism has caused and is causing a number of completely inexcusable deaths each year. These have, unfortunately, not been widely enough publicized; hence, many physicians are still unaware of the dangers of pressure transfusions of this type. The fault has lain not in the use of gases for pressure transfusion but rather in the failure to recognize the necessity for the proper safeguards for such methods. At the Memorial Hospital in New York,[93] and in others, where organized transfusion-therapy teams administer pressure transfusions, the hazard is minimal, but in many hospitals such therapy has been left to someone unfamiliar with its dangers or so occupied with other duties that inadequate attention has been given to the transfusion. In most hospitals gas-pressure transfusions cannot be given with safety. In some hospitals their dangers have been recognized and they have been outlawed. There are three simple alternative methods, of which the last, still in its developmental stage, is the most attractive. The first of these is the employment of a three-way stopcock equipped with two male and one female hubs that can be inserted into the transfusion tubing. Blood can then be pumped manually by means of a 50-cc. syringe into the patient. Five hundred cubic centimeters may be infused with almost complete safety in five to ten minutes by this method. Better than this is the use of the De Florez pump, a handsized pump with an eccentric wheel around which the tubing is wound; by means of the turning of this wheel blood can be forced in by hand under direct observation at the rate of 500 cc. in two to three minutes. These pumps have been used with great success for both intravenous and intra-arterial transfusion in several hundred transfusions performed at the Massachusetts General Hospital. The pump must be "tailor-made" for the tubing and needles of No. 16 caliber or larger must be employed. Plastic bags containing liquid ACD are now in experimental use as whole-blood containers. For rapid transfusion they give great promise. They contain no air and may be squeezed by manual or other pressure for rapid, safe transfusion.

In all methods of pressure transfusion, the use of a large needle is necessary to prevent cell destruction.[84] With the De Florez pump the amount of free hemoglobin has varied from an average figure of 50 to 60 mg. per 100 ml. when a 15-gauge needle has been used to between 500 and 600 mg. for an 18-gauge needle when the blood was pumped as rapidly as possible. It is wise, therefore, on all intravenous sets for operating-room use to have large-caliber needles available. Often, if they are used and the tubing is long enough to permit the full effect of gravity, other methods of pressure transfusion are unnecessary.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 37371

PRESENTATION OF CASE

First admission. A fourteen-year-old boy was admitted to the hospital complaining of dyspnea on slight exertion.

Shortness of breath was first noted by his parents about four years prior to admission but had been subjective only one and a half years. Since then the patient had become dyspneic after walking about 100 yards on level ground; whenever he walked longer distances without resting he became dizzy, and he occasionally noted palpitations. For two years before entry it was necessary to have someone else run bases when he played ball. There was no orthopnea. There was no history of fever, malaise, joint pain or swelling, epistaxis, syncope, noticeable cyanosis, pleurisy, pneumonia or chest pain. He coughed very little but had expectorated a small amount of blood three months before entry.

The patient had been a full-term normal baby and had apparently been healthy and active as a child. There was no family history of heart disease.

Physical examination revealed a pale, minimally cyanotic boy in no distress. The precordium of the left chest bulged, causing slight scoliosis and thoracic asymmetry. The apical beat was in the left midaxillary line in the fifth intercostal space, and there was a palpable thrust and a diastolic thrill. A loud mitral first sound, a Grade III apical systolic murmur and a diastolic rumble with presystolic accentuation were heard. There was a high-pitched diastolic blowing sound in the pulmonary area and a marked diastolic murmur in the fourth interspace along the left sternal border. The lungs were clear. The liver edge was percussed 3 cm. below the costal margin. There was no ankle edema.

The temperature was 98°F., the pulse 100 and the respirations 20. The blood pressure was 110 systolic, 98 diastolic.

Urinalysis was negative. The blood hemoglobin was 15.9 gm. and the white-cell count and differential were normal. An x-ray film of the chest showed emphysema, low diaphragms and a fine network of increased density in both lower lobes. The heart was markedly enlarged, predominantly in the region of the right ventricle, and an unusually prominent right pulmonary artery could be seen (Fig. 1). An electrocardiogram demonstrated a rate of 100, a PR interval of 0.17 second and right-axis deviation. He was discharged after fifteen days' observation on digitalis therapy, with little change in his condition.

Second admission (three years later) for tooth extraction. In the two-year interval the patient was followed in the Cardiac Clinic. Subjectively, he had remained unchanged. The vital capacity was

60 per cent. At one time an irregular pulse was noted, but an electrocardiogram taken three days later was essentially similar to the previous one. Prophylactic penicillin was given, and he had an uneventful course. The sedimentation rate was 10 mm. in 45 minutes and 14 mm. in 1 hour.

Third admission (one year later) for cardiac catheterization. Blood samples showed the following oxygen content: right pulmonary artery 11.5 vol. per cent, or 54 per cent saturation; radial artery, 20.0 vol. per cent, or 94 per cent saturation; right ventricle 11.1 vol. per cent, or 52 per cent saturation; right auricle from 10.5 to 11.7 vol. per cent, or 50 to 55 per cent saturation; and superior vena cava 11.1 vol. per cent, or 52 per cent saturation. A chest film showed the heart to have enlarged rapidly since previous films. The vascular pattern in the lungs had altered, and the right interlobar artery had further increased in diameter and tapered abruptly to a termination. Fine linear densities and a honeycomb pattern were still present in the lower lung fields. The right lower lobe was reduced in size. He was discharged on the second hospital day, subjectively unchanged.

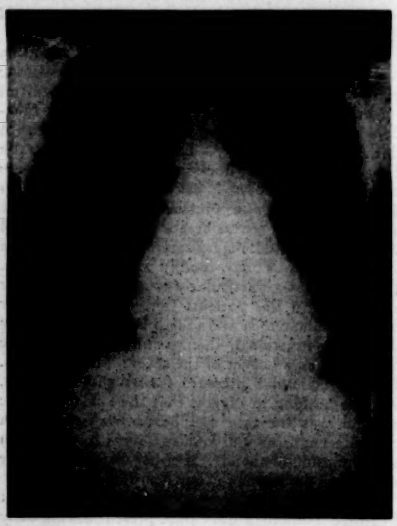

FIGURE 1. *X-Ray Film of Chest Four Years Before Death, Showing Evidence of Rheumatic Heart Disease.*
Note that the right interlobar artery ends by branching into many vessels.

Final admission (one and a half years later, at the age of nineteen) because of ankle edema that was refractory to mercurial diuretics.

The swelling began slowly five months before admission. Exercise tolerance became progressively more limited. Until one month before entry the edema had responded to mercurial diuretics, ammonium chloride and a low-salt diet. One month before entry he developed a "cold" that persisted for three weeks. From that time on the edema had ceased to be affected by the usual treatment.

Physical examination showed a chronically ill boy with distended neck veins and orthopnea. A firm, smooth liver edge was palpated 7 cm. below the costal margin. There was +++ ankle edema, bilateral pleural effusion and evidence of ascites. The heart rate was grossly irregular. The heart was enlarged beyond the midaxillary line in the fifth interspace. Murmurs and thrills were unchanged from the previous admissions. The blood pressure was 100 systolic, 70 diastolic.

The serum sodium was 136 milliequiv. and the chloride 103 milliequiv. per liter; the nonprotein nitrogen was 32 mg. and the van den Bergh 2.6 mg. direct, 3.2 mg. total, per 100 cc.

The patient was placed on a low-sodium diet and received 8 cc. of a cation-exchange resin twice a day and frequent intramuscular injections of Mercuhydrin. At the end of two weeks there had been no significant diuresis or other improvement. Temporary response followed thoracentesis and oxygen therapy, with a diuresis occurring, but fluid again accumulated. Cortisone, 75 mg. daily for six days, brought no obvious improvement. On the thirty-ninth hospital day, three days after cortisone was stopped, the patient was found unresponsive on the floor beside his bed. There was no external head injury and no localizing neurologic signs. The blood pressure, temperature, pulse and respirations were unchanged. He died four hours later without regaining consciousness.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. PALMER*: In this patient I am dealing with the problem of anoxemia that may have been due to heart disease, respiratory disease or anemia. As there was no anemia and no evidence of any primary respiratory disease, I am dealing with heart disease. In this age group it is a 99-to-1 chance that heart disease is rheumatic.

I should like to ask Dr. Hanelin if he can identify the left auricle in the x-ray films. Could the enlargement reported in the region of the right ventricle actually have been due to a huge left auricle? Also, I should like to know whether the pulmonary artery was aneurysmal, large or merely prominent.

DR. JOSEPH HANELIN: The chest films taken during the first admission five years before death show emphysema, large main, right and left pul-

*Physician, Massachusetts General Hospital.

monary arteries and a fine network throughout the lungs, somewhat more marked at the bases. There is evidence of left-auricular enlargement in addition to ventricular enlargement. However, the left auricle is not huge; the right ventricle preponderates (Fig. 1). Particularly well demonstrated in the right-anterior-oblique view is the prominent outflow tract of the right ventricle.

Dr. William Eyler, who interpreted the films taken during the third admission, one and one-half years before death, pointed out the further enlargement of the right interlobar artery and its changed contour (Fig. 2). It tapers to a conical distal ex-

FIGURE 2. *X-Ray Film of Chest One and a Half Years Before Death.*

The heart has enlarged further. Note change in size, shape and configuration of right interlobar artery, which now appears even more dilated and which terminates abruptly.

tremity, and only a few slender vascular shadows extend into the right lower lung as compared to the previous film, in which there is a smooth continuity between the interlobar artery and the branches that proceed downward. The heart is considerably increased in size. There are interesting transverse shadows in the lower portions of the lungs that probably represent congested lymphatics.

DR. PALMER: I dislike hearing you mention the lymphatics' extending out to the lower portions of the lungs. I had certainly not considered any form of tumor.

DR. HANELIN: I do not wish to imply that the transverse densities may represent lymphatic spread of tumor in this case. Engorgement of lymphatics is not uncommon in pulmonary congestion.

The films taken during the final admission demonstrate a large right-pleural effusion, with fluid extending into the major septum. There is some loss of volume of the right lower lobe. A small amount of fluid is present at the left base. It is impossible to determine the heart size because of the changes in the pleura.

DR. PALMER: In arriving at a diagnosis in this case one must be guided not only by the positive findings but also by some negative findings. The patient was not a blue baby, and nothing unusual was noted at the time of birth or in early childhood. However, the negative rheumatic history is not important, as it is negative in about 50 per cent of proved cases of rheumatic heart disease.

The patient had a loud mitral first sound, a rumbling diastolic murmur and a loud systolic murmur at the apex, which to me means mitral stenosis. A mitral diastolic murmur may be functional, due to aortic regurgitation, although in this case that is unlikely. There was a narrow pulse pressure, but that does not positively exclude aortic regurgitation. I have seen patients with similar narrow pulse pressures, murmurs at the base and severe mitral stenosis who actually had aortic stenosis and regurgitation; that is, a degree of aortic stenosis may modify the pulse pressure. There was not a particularly loud systolic murmur at the base in this patient. The diastolic murmur in the pulmonic area and fourth left interspace may have been functional, due to functional pulmonic regurgitation, an effect of the severe mitral stenosis. The narrow pulse pressure favors this diagnosis. There is nothing to suggest that the apical diastolic murmur was the rare sort heard transiently with an acute nephritis and sudden severe hypertension or with profound anemia. If either diastolic murmur was functional it was the one heard at the base.

There was a chest deformity, which suggests that a cardiac lesion may have been present during early life; this does not necessarily mean from birth. In a growing child severe mitral stenosis may deform the chest. Chest deformity is likely to occur in combination with an auricular-septal defect and mitral stenosis. Let us consider this combination of heart lesions. The absence of a loud systolic murmur, particularly high toward the base, makes me doubt its presence. The left auricle was prominent or enlarged by x-ray examination. This is extremely important. In the Lutembacher syndrome, — auricular-septal defect and mitral stenosis, — the left-auricular pressure of mitral stenosis is minimized by the septal defect; hence auricular enlargement is not found. Therefore I conclude that in this case there was not a significant auricular-septal defect.

I believe that this patient had severe rheumatic heart disease and mitral stenosis, and that he had

had it from an early age. There was an increased pressure in the pulmonic circulation, and he had had the disease long enough to produce hypertensive vascular changes, which in themselves caused anoxemia and contributed to the minimal cyanosis noted. If a diagnosis of functional pulmonic regurgitation is ever to be made, this is the type of case in which it should be made. The only "fly in the ointment" is the fact that the diastolic murmur was heard along the sternum and was not localized in the pulmonic area. Because of the position of the valves in relation to the body surface, it is not always possible to determine accurately the source of a murmur.

I have been wondering why the cardiac catheterization was done. It is hazardous for the patient and difficult for the physician. I think the physicians may have been considering the possibility of congenital heart disease because of the large pulmonic artery. It may have been done to determine the blood flow, with valvulotomy or other surgery in mind. At any rate, the conclusions to be drawn from the results should be simple. There was no significant difference between the volume per cent of oxygen in the vena cava (11.1) and the right auricle (10.5 to 11.7), — slightly less than 2 volumes per cent is the normal variation, — nor was there any significant difference between the right auricle and the right ventricle or between the right ventricle and right pulmonary artery. If this test was done properly, it indicates that there was no communication between the right and left sides of the heart. But do I really know that? Did the physician get fair samples, with good mixing? Or was the patient in heart failure, with enough hypertrophy of the right side of the heart so that the pressure was sufficient to prevent the left-right shunt? That is a possibility. As I have concluded already that there was not an auricular or ventricular-septal defect, these findings encourage me.

I think this patient had rheumatic heart disease with mitral stenosis of a severe grade, congestive heart failure, especially on the right side, and passive congestion with an enlarged liver. There is also a question whether he had cardiac cirrhosis; I think he may have. Moreover, I think it is reasonable to say that he had functional pulmonic regurgitation, with an aneurysmal dilatation of the pulmonic artery. There was hypertension of the pulmonic circulation, and I suspect that he had some vascular changes due to this. There may or may not have been active rheumatic pneumonitis and carditis. He certainly had old pulmonary infarctions, and he may have had a large thrombosis in the main vessel, with scarring, collapse and chronic change in the right lower lung. He must have had tricuspid dilatation and may actually have had tricuspid disease.

The physicians apparently believed that the protracted failure and progressive downhill course were due to active rheumatic infection, as they gave him cortisone. I should like to ask Dr. Mallory if a course of cortisone modifies the pathologic picture to the extent that the pathologist cannot tell whether or not there has been an active rheumatic infection.

What was the cause of death? Why did the patient die at the exact time that he did without any increase in respiration? I think he may have had an acute and large pulmonary embolus, but I should have expected the respirations to be increased and the patient to be in marked shock. Usually patients with mitral stenosis are in a terminal state for two or three days before death. It is very strange that he should have died so suddenly without any particular observable change in his condition. Mottled cyanosis, if noted, would be significant. Sometimes patients with mitral stenosis have a ball thrombus that completely obstructs the mitral orifice. How they continue to live at all I do not know, but they do — sometimes long enough to show peripheral mottled cyanosis and even peripheral gangrene.

Dr. Alexander Leaf: Perhaps I can explain our reasons for using cortisone in this patient. Some twenty years ago Newburgh and others[1] stated the principle that extracellular fluid volume cannot expand without retention of sodium. The corollary of this, — namely, that a reduction in body sodium will result in a proportional decrease in extracellular fluid volume, — has been the rationale of much of our present therapy of edema. This patient had been treated vigorously with a low-sodium diet, ammonium chloride, mercurial diuretics and cation-exchange resin — all measures aimed at reducing body sodium. However, like many others, he lost body sodium but failed to lose water proportionately and wound up with a low serum sodium, concentrating less than 120 milliequiv. per liter. How one can develop such low serum-sodium concentrations is rather a puzzle when one considers the normal physiology of water excretion.

The work of Verney[2] has clearly shown that the supraopticohypophyseal mechanism is sensitive to changes in effective total solute concentration of the serum. An increase in serum total solute concentration, such as occurs during dehydration or on infusion of hypertonic solutions, stimulates the posterior pituitary gland through osmoreceptors to elaborate antidiuretic hormone (ADH). ADH acts on the kidneys, causing formation of a concentrated urine, with resultant conservation of body water. The dilution of the serum that follows water administration inhibits posterior-pituitary activity, allowing diuresis of a dilute urine, thus ridding the body of the administered water load. If sodium is the major osmotically active constituent of the serum, a reduction in its concentration should lead to a dilute extracellular

fluid. But a dilute extracellular fluid should inhibit the posterior pituitary gland, allowing a diuresis of a dilute urine with return to normal of the serum sodium. Why does this not occur? Our present evidence points to an overactivity of the posterior-pituitary antidiuretic mechanism in the situation. Patients such as this have a dilute serum but a concentrated urine and fail to have a diuresis after water administration. This difficulty in water excretion is also shared with the patient with Addison's disease. In the latter, administration of cortisone corrects the disturbance, presumably by inhibiting the excessive posterior-pituitary activity. Thus cortisone was administered to this patient in the hope that the disturbance in water excretion would be corrected and the patient enabled to reduce the edema fluid by at least that increment which was due to the excessive water retention causing sodium dilution. Our hope was not confirmed.

DR. ERNEST CRAIGE: May I say a word about the cardiac catheterization? Those who followed this patient in the Cardiac Clinic for four years were not as shrewd as Dr. Palmer in excluding the presence of an interauricular septal defect. The presence of large pulsating pulmonary arteries seen by fluoroscopy, together with the other physical signs, made us think that the patient had Lutembacher's syndrome — mitral stenosis with an interauricular septal defect. With the increasing availability of mitral surgery, it was thought best to delineate the diagnosis as carefully as possible. The cardiac catheter was observed by fluoroscopy to pass through the right auricle and ventricle in the usual manner. After passing a short distance into the right pulmonary artery, the catheter encountered some obstruction. When this was discussed later with Dr. Eyler, it was apparent that the obstruction in the pulmonary artery was at a point where he had suspected a thrombosis in the x-ray film of the chest.

Several samples of blood were taken from the right auricle; there was no difference in their oxygen content from that of blood obtained from the superior vena cava. It was concluded that there was no evidence by catheterization of an interauricular septal defect. The pressure in the pulmonary artery was very high, being 160 systolic, 55 diastolic, with a mean of 90 mm. of mercury.

DR. PALMER: I did not mean to criticize the use of this technic in this case, but I suggested that it may have been done with a view to possible valvulotomy.

CLINICAL DIAGNOSES

Rheumatic heart disease, active, with mitral stenosis, regurgitation, auricular fibrillation and congestive failure.
?Cerebral embolus.

DR. PALMER'S DIAGNOSES

Rheumatic heart disease with mitral stenosis, severe.
Congestive heart failure.
Cardiac cirrhosis.
Pulmonary vascular changes, hypertensive.
Pulmonary thrombosis.
Pulmonary infarction.
?Active rheumatic infections of heart and of lungs.

ANATOMICAL DIAGNOSES

Rheumatic heart disease with mitral stenosis, severe.
Pulmonary embolism with superimposed thrombosis, very old, right pulmonary artery and branch to left upper lobe, old.
Cardiac hypertrophy, right side, marked.
Cirrhosis of liver, cardiac.
Pulmonary arteriosclerosis, marked.
Pulmonary fibrosis.
Pulmonary infarct, healed, old, right basal segment.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: There were no particular surprises in the findings at post-mortem examination. The heart was very much enlarged, weighing 510 gm., which would be very big for a boy of this age. The hypertrophy was predominantly in the right ventricle, and the major valvular lesion was a severe mitral stenosis. There were also traces of old rheumatic affection of the aortic and tricuspid valves, but it did not appear obvious from the appearance at autopsy that any severe degree of functional deformity was present in either of these two valves. The right ventricle was very much hypertrophied and markedly dilated. It was as thick as the left ventricle, measuring 11 mm. in cross-section. We did not find any evidence of active rheumatic infection. I cannot answer Dr. Palmer's question about whether such evidence could have been abolished by the cortisone treatment or not. It is a justifiable suspicion that that might have been the case, and we would very much like to know the answer ourselves.

The pulmonary artery showed very severe changes. There was a patchy atherosclerosis of all the major divisions, and there was a large, well organized thrombus measuring 12 by 2 by 2 cm. occluding the major branch of the right lower lobe, which undoubtedly was the lesion observed radiologically. A second large thrombus, less old than the one I have already described though by no means entirely fresh since it was firmly adherent, almost completely occluded the pulmonary-artery branch to the left upper lobe. It is always difficult and sometimes quite impossible to decide whether the clots found within a pulmonary artery represent emboli that have become adherent or thrombi that have formed in situ. Recent experi-

mental work has shown that all the conditions formerly regarded as pathognomonic of thrombus formation can develop as the result of embolism and secondary organization.[3] Throughout the lungs, particularly in the left lower lobe, there was very marked fibrosis of a rather unusual appearance. It seemed to be primarily a fibrous thickening of the interalveolar septa, with more or less complete obliteration of the alveolar-wall capillaries in many areas. I doubt that it is possible, from looking at this fibrous scar, to determine with certainty the nature of the acute process in the lung of which this is the end result. There are many possibilities, such as old infarction and healed pneumonitis. However, an elastic-tissue preparation showed whorls of elastic without alveolar arrangement characteristic of healed infarction.[4]

Another finding that I believe may have some functional significance in this man's symptomatology was the presence of very marked liver changes. On gross examination the liver showed granularity and a marked increase in firmness and toughness that made it quite difficult to cut with a knife; microscopically, I believe it could be fairly described as a cardiac cirrhosis of the liver. At least a portion of the edema, ascites and so on may probably have been due to hepatic insufficiency as well as to the severe right-sided heart failure that we know he had.

We were unable to find anything in the brain to explain the sudden terminal episode. There was no skull fracture, no evidence of any severe grade of cerebral contusion or laceration and no vascular occlusions due either to sclerosis or to emboli.

DR. PALMER: That was not a ball thrombus in the mitral valve?

DR. MALLORY: No; there was a rather large thrombus in the auricle, but it seemed firmly attached to the auricular wall.

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CASE 37372

PRESENTATION OF CASE

First admission. An eleven-year-old boy was admitted to the hospital because of fatigue, abdominal pain, nausea and weight loss.

Four months before admission the patient began to be weak and fatigued. Shortly thereafter he had postprandial abdominal pain, severe anorexia, abdominal distention, nausea and occasional vomiting during meals. He also noticed that his stools were lighter in color and his urine darker than usual. Seven weeks before entry he was seen in the Out Patient Department. He was afebrile and slightly icteric. He was put to bed at home and a high-calorie, high-protein, high-carbohydrate diet prescribed. When he was examined one week later in the Out Patient Department slight hepatosplenomegaly was thought to be present. The bilirubin was 2.2 mg. direct, 2.4 mg. total, per 100 cc. The cephalin flocculation was ++++ in twenty-four and forty-eight hours and the hemoglobin 12.4 gm. Gradual improvement occurred, with clearing of the icterus. Two weeks before entry the jaundice, nausea and abdominal distention with gaseous eructations recurred. Frequent epistaxes occurred and a folliculitis of the anterior aspect of the lower extremities developed. After slight improvement at home, admission to the hospital was decided on for evaluation of symptoms.

He had had virus pneumonia and measles at the age of four, chicken pox at the age of six, an episode of joint pains and abdominal distress at the age of seven and adenoidectomy at the age of eight years. Except for frequent head colds in both winter and summer, his general health had been good until the onset of the present illness.

Physical examination revealed a chronically ill-appearing boy who was 4 feet, 11½ inches in height and weighed 92 lb. The skin and scleras were mildly icteric and a widespread folliculitis was present over the lower extremities. The abdominal veins were more prominent than usual and the abdomen was distended. A definite fluid wave was present. The liver and spleen were palpated 1 cm. below the costal margin. No abdominal masses or tenderness were present. The heart and lungs were normal.

The temperature was 99°F., the pulse 120 and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine urobilinogen ranged from 8.6 to 1.5 Ehrlich units, but no bile or other urinary abnormality was noted. Examination of the blood showed a hemoglobin of 11.9 gm. and a white-cell count of 6200. with 38 per cent neutrophils, 55 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The fasting blood sugar was 85 mg., the nonprotein nitrogen 17 mg., the bilirubin 2.0 mg. direct and 2.8 mg. total, the cholesterol 134 mg., the cholesterol esters 36 mg., the phosphorus 3.7 mg., the alkaline phosphatase 11.3 units, the thymol turbidity 5 units, the total protein 5.49 gm., the albumin 2.38 gm. and the globulin 3.11 gm. per 100 cc. (albumin-globulin ratio, 0.8); the sodium was 135.3 milliequiv., the potassium 5.7 milliequiv., the chloride 106 milliequiv. and the carbon dioxide 31 milliequiv. per liter. The prothrombin time was 40 seconds (normal, 19 seconds), the cephalin flocculation ++++ in twenty-four hours, the thymol flocculation +++ and the bromsulfalein retention 30 per cent in forty-five minutes. Heterophil agglutination and stool cultures were

negative. X-ray studies of the abdomen suggested a large liver and spleen. A barium-swallow examination was negative. An x-ray film of the chest showed elevation of the diaphragms. An electrocardiogram revealed a rate of 105, a PR interval of 0.10 second, a QRS interval of 0.06 second and a QT interval of 0.36 second.

Dietary therapy was continued in the hospital, with vitamin supplements and bed rest. The patient showed no improvement and developed increasing ascites. While in the hospital he received a course of adrenal-cortical extract, cortisone for three weeks, aureomycin, Chloromycetin, streptomycin, penicillin, blood transfusions and vitamin K_1 oxide. The latter two had little effect on the elevated prothrombin time. Mercurial diuretics and ammonium chloride failed to produce a diuresis, and frequent paracenteses were required, in some of which up to 4700 cc. of fluid was removed. After two of the taps he developed fever and abdominal pain, which responded to antibiotics. The total protein of the ascitic fluid was 450 mg. per 100 cc. No improvement in the patient's clinical condition or liver function was noted after five months of hospitalization. He was discharged on a high-carbohydrate, high-protein, low-salt diet, with supplementary vitamins.

Second admission (two days later). The patient was readmitted to the hospital three hours after the onset of shaking chills and abdominal pain with subsequent watery stools.

On examination the pharynx was moderately injected. The abdomen was distended; a fluid wave could be elicited, and there was tenderness in both upper quadrants and in the epigastrium. The liver was not felt, but the spleen was palpated 4 cm. below the costal margin. Drainage was noted from the most recent paracentesis site. Slight ankle edema was present.

The temperature was 102°F., the pulse 120 and the respirations 25. The blood pressure was 90 systolic, 60 diastolic.

The hemoglobin was 14 gm. and the white-cell count 22,500, with 88 per cent neutrophils. Urinalysis was negative. Atypical forms of *E. coli* were recovered from blood culture.

Response to penicillin was good, and the patient was discharged afebrile on the sixth hospital day.

Third admission (three weeks later). Two weeks before entry 5500 cc. of straw-colored fluid with a specific gravity of 1.012 was removed from the abdomen. The day before admission the patient had a "running nose," a slight cough and a temperature of 100°F. On the morning of admission he appeared improved, but a half hour after the mid-day meal he suddenly developed chills and fairly severe abdominal pain.

On admission he was acutely ill and had a temperature of 103.4°F., a pulse of 136 and respirations of 22. Again the pertinent physical findings were abdominal distention and diffuse abdominal tenderness.

Examination of the blood revealed a hemoglobin of 12.9 gm. and a white-cell count of 11,850, with 81 per cent neutrophils. The total protein was 4.78 gm. and the bilirubin 0.9 mg. direct, 1.1 mg. total, per 100 cc. The cephalin flocculation was +++ in twenty-four and forty-eight hours, and the prothrombin time 50 seconds (normal 17 seconds). Type 18 pneumococci were recovered from blood culture.

The patient responded well to penicillin and streptomycin and was discharged afebrile on the tenth hospital day.

Final admission (two months later). In the interim between admissions the patient had required nine paracenteses in the Out Patient Department because of the rapid reaccumulation of ascites. One week before entry he complained of muscle cramps; the serum sodium was found to be 114 milliequiv. and the chloride 85 milliequiv. per liter. The low-salt diet was discontinued. At that time paracentesis was performed. The ascites reaccumulated rapidly after this, and by the day of admission he had severe abdominal discomfort.

Physical examination revealed that the boy was cachectic, with a tremendously distended abdomen. In addition, there was upper-abdominal tenderness and a fluid wave could be elicited. No masses or enlarged organs were noted.

The urine was normal. Examination of the blood showed a hemoglobin of 14.4 gm. and a white-cell count of 32,600, with 85 per cent neutrophils. The sodium was 109 milliequiv., the potassium 6.6 milliequiv., the chloride 80 milliequiv. and the carbon dioxide 17.4 milliequiv. per liter. The nonprotein nitrogen was 30 mg. and the total protein 3.4 gm. per 100 cc. The urine chloride was 26 milliequiv. and the sodium 0.5 milliequiv. per liter. An electrocardiogram showed a regular rate ranging from 90 to 115, PR intervals from 0.13 to 0.11 second, QRS intervals from 0.06 to 0.11 second and QT intervals from 0.36 to 0.30 second. In one tracing the T waves were noted to be slightly lower than normal.

A paracentesis was performed shortly after admission, with removal of 10,500 cc. of fluid. Plasma, physiologic saline solution with and without potassium, and dextrose in water were infused. Four gm. of salt was added to the house diet. The patient gradually grew weaker and drowsy, and on the eleventh hospital day he lapsed into unconsciousness and died.

Differential Diagnosis

Dr. Rita M. Kelley*: In summary this was a boy who had previously been well and who then developed a disease complex that progressed until

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four months after the appearance of symptoms the disease was totally unresponsive to all attempts at therapy.

I would like to simplify my problem at the beginning, probably to my later regret, by localizing this disease to a single organ — namely, the liver. It seems to me that all the positive features of the history and the physical examination and chemical and laboratory findings, together with the course of the disease, plus the negative findings, which were either stated or implied by their failure to be stated, can all be explained by primary liver disease and the complications thereof. In so doing I am ruling out a great many diseases that may produce this picture as part of their generalized manifestations involving multiple organ systems, but in such diseases a course so predominantly that of acute liver disease would be very unusual. There was no evidence to suggest hepatic invasion and destruction by disease such as lipoidosis, the glycogen-storage diseases, amyloidosis, leukemia, lymphoma or metastatic cancer. In the case of the latter, something like metastatic neuroblastoma could conceivably be limited to the liver and cause this picture, but that would be so unlikely that I think I am justified in eliminating it.

At this point, may I see the x-ray films?

DR. JAMES J. MCCORT: In the chest examination made on the first admission, both lungs are clear. The heart is not enlarged. There may be a slight amount of fluid along the costophrenic sinuses. Both leaves of the diaphragm are elevated, undoubtedly because of the ascites. A small amount of barium in the esophagus fails to disclose any varices. The bones of the thoracic cage show no abnormality. The films of the abdomen, obtained at the same time, show enlargement of the spleen to approximately twice normal size. The liver is only questionably enlarged. The stomach is displaced toward the midline by the enlargement of the spleen. There is some hazy increase in density of the abdomen, which is consistent with increased intraperitoneal fluid. Further x-ray examinations of the chest were made at intervals of two months. They show no change in the lung fields, which remain clear throughout the patient's hospital course. One notes that the leaves of the diaphragm are subsequently higher on each x-ray examination, indicating an increasing amount of intra-abdominal fluid, and at the time of the last examination both the liver and spleen are obscured by the enormous amount of fluid filling the abdomen. We are unable to visualize the kidneys.

DR. KELLEY: I think these x-ray findings partially justify my decision to confine my discussion to diseases of the liver; at least, there is no evidence of widespread malignancy or any other generalized disease that shows up by x-ray examination.

I shall attempt to reconstruct the events that led to the patient's loss of hepatic function. The onset of the disease was apparently rather abrupt, with the appearance of weakness and fatigue rapidly followed by a series of symptoms that are fairly common when the liver is involved in acute disease of an inflammatory or degenerative type — that is, postprandial pain, severe anorexia, abdominal distention, nausea and vomiting. Such symptoms as these are attributed by Himsworth[1] to the acute distention of the liver that occurs with rapidly developing disease. Objective evidence of liver disturbance appeared in the form of light stools and dark urine. These symptoms, although it is not definitely so stated, apparently persisted in some degree from the time he was first seen in the clinic to the time of admission some nine weeks after the onset of symptoms. At that time there was unequivocal evidence of active parenchymatous liver disease, with slight icterus confirmed by the van den Bergh test, the slight hepatosplenomegaly and the strongly positive cephalin-flocculation test. Also typical of an acute process in the liver is the fact that he made some temporary response to the generally accepted types of treatment of this condition — namely, complete bed rest and a high-protein, high-carbohydrate diet. The fact that all the symptoms recurred after a few weeks is also characteristic of a progressive type of acute liver disease.

Next I wish to consider the possible etiology of this presenting picture, which we are accepting as an acute derangement of the liver parenchyma of either inflammatory or degenerative nature or possible a mixture of both. It is important to decide whether this disease occurred in a previously normal liver or in a liver that perhaps had a congenital defect or that had been damaged earlier in childhood. I have little information on which to base this latter premise except the poorly described episode of abdominal and joint pain that occurred four years prior to this admission. Without knowing any further details of the severity, the duration or the symptomatology of this episode, I do not think I can say it was contributory to the present illness, although I recognize that it could possibly have caused some liver damage.

None of the diseases that were mentioned in the past history are those that are usually accompanied by liver damage, particularly of a permanent nature; therefore I cannot implicate any of these diseases. There are rare cases of cirrhosis in children that are diagnosed in retrospect as possibly having originated in colon-bacillus infections or severe streptococcal infections, particularly scarlet fever, but again there was no history to justify this conclusion. Congenital syphilis can be mentioned only to be ruled out. Sometimes the picture of hepatitis can dominate congenital syphilis, but that is quite unusual. There is also the possibility of prolonged poor nutrition, which can predispose the liver to severe insult, but again nothing in the history

justifies the assumption of prolonged nutritional deficiency in the liver.

I am therefore left with two possibilities. The first one is that this was the first manifestation of a subclinical cirrhosis that occurs on an idiopathic basis in children. This has been called by Moon[2] an atypical portal type of cirrhosis and is very similar to portal or Laennec's cirrhosis in the adult. Although this disease usually develops more insidiously, it can present just such a picture and pursue the same course as was present in this case. The grounds here are not adequate to rule out this particular type of disease. I would like to relegate it to a second place, however, in my choice of diagnoses. One small point against a long-standing liver disease is that the hemoglobin was normal when the patient first came to the hospital. If he had had a long-standing fibrotic type of disease, I should expect him to have had a macrocytic type of anemia.

The second and to me much more plausible possibility is that of an acute hepatitis that arose in a previously normal liver. There are two kinds of agents that may precipitate this type of picture: toxic and infectious. In the former category fall such chemicals as phosphorus, chloroform, carbon tetrachloride, arsenicals and sulfonamides. I am sure that this history was carefully elicited in this child, and failure to mention any such exposure is tacit agreement with me that there was none.

There is a large group of infectious diseases that are accompanied by acute hepatitis as part of the generalized disease picture. My original choice of concentrating on the liver automatically eliminates these, but I think I should mention that a very acute and predominantly hepatic type of picture can rarely occur in such diseases as mumps, virus pneumonia, infectious mononucleosis, brucellosis, Weil's disease and a host of other diseases to which children are prone. Again, nothing in this history or general examination suggested that this child had any such disease process, and I should like to eliminate these. That brings me to the infectious agents that affect the liver primarily. Once again a negative history comes to my aid, in that there is no history of recent inoculations or injections of any kind that might suggest the homologous-serum-jaundice type of disease.

So I am left with acute viral hepatitis as the most likely explanation for this first acute episode. The presenting and persistent symptoms, — the mild icterus, the hepatomegaly and splenomegaly and the strongly positive cephalin flocculation at the time of the first appearance, — are all compatible with this diagnosis. The physical and biochemical conditions of the patient when he was admitted several weeks later all suggest that there was a subsequent change in the disease pattern from one of an acute hepatitis to a more chronic type of disease, and there is eloquent evidence that an unrelenting process had been set up by the first insult and had proceeded inexorably toward death. Because of the presence of prominent abdominal veins and ascites when the patient was first admitted, some four months after the onset of the disease, I assume that he developed some portal hypertension in the interim. However, the ascites cannot be explained by portal hypertension alone; Himsworth[1] states that there must be a lowered albumin as well in order to produce ascites. This child had a definitely low serum albumin. The third possible factor in the production of ascites is that the sick liver failed to detoxify the antidiuretic principle and therefore led to a more rapid accumulation of fluid.

That failure of many of the vital functions of the liver parenchyma had already occurred at the time of the third admission is abundantly apparent. For instance, the folliculitis on the extremities probably represented failure to manufacture vitamin A. The epistaxis can be attributed to the prolonged prothrombin time, which failed to respond to large doses of vitamin K. There was also a marked deficiency in the manufacture of cholesterol esters and of urea, which was exemplified by the low nonprotein nitrogen. The patient also demonstrated increased bromsulfalein retention and urobilinogen excretion, a moderately elevated alkaline phosphatase and a reversed albumin-globulin ratio, all of which are further evidence of advanced cellular dysfunction.

The remainder of the physical examination, the laboratory data, the x-ray findings and the electrocardiogram demonstrate once more that all of the patient's primary disease was localized to the liver. It can be explained by transition of the original lesion of acute hepatitis, which is primarily an inflammatory and necrotic process, to a more chronic and fibrotic type of process with an attempt at regeneration of the liver — that is, cirrhosis superseding an acute hepatitis. I think the type of cir-

rhosis that will be found here is the so-called postnecrotic type, which has been described by Dr. Mallory[3] as a sequel to severe prolonged acute infectious hepatitis. The other possibility of an atrophic portal type of cirrhosis cannot be ruled out, since the same course could be pursued by this type of disease, and I shall have to leave that as the second choice. Kunkel[4] has stated that the postnecrotic type, as opposed to the portal type, is characterized by lack of response to nutritional and dietary therapy, which this child demonstrated. He also demonstrated a marked resistance to a really formidable array of therapeutic agents, to none of which could he be expected to respond with this condition. The last months of his life were marked by additional evidence of steadily advancing cirrhosis, with increasing accumulation of fluid, the removal of which enhanced his natural tendency to low serum protein and also produced a marked electrolyte loss. Moreover, the liver diminished in size at this time, and the spleen appeared to be enlarging. All these signs are compatible with a cirrhotic process.

The last month of his life was punctuated by the rapid appearance of rising fever, shaking chills, abdominal pain and leukocytosis. These symptoms may occur in severe, advancing liver disease without any evidence of infection whatever, and are quite commonly seen in adult portal cirrhosis. They could also be explained by intraperitoneal bleeding around the liver and spleen, due to the low prothrombin time and causing a perisplenitis. However, because of the fact that he responded to antibiotics on most occasions, and because of the marked proneness of these patients to infection and the ready route of infection through the previous paracentesis sites, I prefer to assume that these were explained by repeated episodes of peritonitis, perhaps with pneumococci or other agents. Two blood cultures show that during at least two of these episodes there was an accompanying septicemia. Although there are no reports of cultures on the peritoneal fluid to support me, I think that peritonitis is probably the most likely explanation for the acute abdominal pain and fever.

My diagnosis, therefore, is postnecrotic cirrhosis following an acute and severe infectious hepatitis. Since idiopathic portal cirrhosis cannot be completely ruled out by any means known to me, I shall have to leave it in as a second choice. I expect there was evidence of repeated episodes of peritonitis, probably without an acute peritonitis at the time of death. Although renal disease is extremely common in death from hepatic failure, there is a good deal of evidence that the child's kidneys were not damaged. He had negative urine reports, a normal nonprotein nitrogen until the end and some evidence, in the very low excretion of sodium and chloride, that the kidneys were attempting to conserve the electrolytes in which he was so deficient.

Dr. Arthur B. French: We had quite a good argument about the character of this disease. It was pointed out that the first serum albumin was already quite low, and for that reason there was some belief that the disease had been of longer duration than the original episode of jaundice. It was clear that there was chronic liver disease as we followed his course. It was heartbreaking to see this young boy pursuing a steady downhill course, with progressively increasing ascites. We believed that it was a postnecrotic cirrhosis on the basis of a chronic infectious hepatitis and that the terminal episode was probably precipitated by the low-salt syndrome that necessitated the last admission. He died rather suddenly in cholemia.

Dr. John T. Quinby: I would like to ask if primary viral hepatitis tends to go on to cirrhosis more frequently in the older patient and if complete recovery is more common in the younger patient.

Dr. Kelley: I think that is true. According to one series, acute infectious hepatitis in children is a limited process, which puts this child in an adult category.

Clinical Diagnosis

Infectious hepatitis with progressive liver failure.

Dr. Kelley's Diagnoses

Postnecrotic cirrhosis.
Repeated episodes of peritonitis.

Anatomical Diagnoses

Postnecrotic cirrhosis.
Splenomegaly.
Ascites.
Hydrothorax, bilateral.

Pathological Discussion

Dr. Tracy B. Mallory: The findings at autopsy are, I believe, entirely consistent with the

diagnosis proposed by Dr. Kelley and likewise made by the house service — yet I know I would have a very difficult time justifying such a diagnosis to a group of inquisitive medical students, who would point out that the lesions found are not what the textbooks describe. The microscopical picture is certainly puzzling, and I am very glad that Dr. French did not do a punch biopsy one or two months before this boy's death and ask me to make a diagnosis at that time. I doubt that I could have done it on a small fragment of tissue. When a viral hepatitis progresses into a scarred fibrotic or cirrhotic liver, one expects to find a very characteristic example of the postnecrotic type of cirrhosis — in other words, to find very large areas of scarring from which all the parenchymal tissues, especially the liver cells, have disappeared and virtually nothing remains but the endothelium of the sinusoids and the continuous reticulum along the sinusoidal walls, with a variable degree of inflammatory infiltration. In other parts of the liver one expects to find relatively large and unusually sharply circumscribed nodules of liver cells, which have been variously interpreted as islands of regeneration or islands of persisting liver parenchyma. These islands are likely to be in the range of 5 to 10 mm. in diameter, — sometimes even larger, — and the multiple small granules 2 to 3 mm. in diameter characteristic of ordinary Laennec's portal cirrhosis are not seen. In this case there were some of the large islands of liver cells, but there were also a great many small granules; hence the gross picture does not clearly fit into either category. The microscopical picture was particularly confusing, in that in the scarred areas, where one ordinarily expects to find only connective tissue and a few preserved small bile ducts, there were a great many tubules about the size of bile ducts but composed of cells that have all the histologic characteristics not of bile duct cells but of liver cells. Some of these cells are extremely atypical in appearance; many of them contain several nuclei, and the nuclei frequently show giant nucleoli, so the cells have many of the features that are associated with neoplastic disease. I think it would be quite possible, on a limited inadequate biopsy of this liver, to have made the diagnosis of carcinoma rather than of regenerating liver tissue. With the entire liver to examine, however, it was at once obvious that no tumor was present. We do know that of all tissues in the body liver regenerates more rapidly after injury than any other, and a great many of the so-called cytologic characteristics of malignancy are perhaps nothing more than the characteristics of excessively active growth — so I do not think it is particularly surprising that features simulating neoplastic disease sometimes should be seen.

Aside from the liver, comparatively little of interest was found at the post-mortem examination. The spleen was enlarged, weighing 310 gm. Ascitic fluid was still present. It was clear and did not show any evidence of active peritoneal infection at the time of autopsy. Moreover, we could not find any peritoneal adhesions or plaques of thickened peritoneum, such as might have been expected if the patient had had one or two transient attacks of peritonitis, as was suggested by the clinical history.

DR. FRENCH: This patient was one of four children under the age of fifteen whom we have seen this spring who had liver biopsies that showed postnecrotic cirrhosis. This was the only child who has died.

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. . . a scholar . . .
Exceeding wise, fair spoken, and persuading.
Henry VIII

F. Parker, Jr. — so he always signs his name — resigned from the post of pathologist-in-chief at the Mallory Institute of Pathology, Boston City Hospital, on July 17, 1951, after thirty-one years of devoted service to the hospital, his staff and — to his delight and to their good fortune — occasional students of the Harvard Medical School. Any eager, bright and inquisitive student, bent on learning all he could in a short time, found in him an almost inexhaustible store of knowledge, and to such men he gave his all. Occasionally a skeptic would question, let us say, the diagnosis of Hodgkin's paragranuloma because he could find no Reed-Sternberg cells. If the skepticism was tinged with the slightest unbelief F. Parker, Jr., would take the slide and in perhaps ten seconds swing the eyepiece to one side and say, very softly: "How do you like that one?" Those who went through this experience emerged wiser and happier men.

To many, retirement means that and no more. But to the Boss, as he is always known at the Mallory (and if the truth be out, in scores of pathological laboratories the country over), it can mean but a greater opportunity to learn and to study. His mind is too active, his interests too catholic, his nature too forceful, his genius too great to have it otherwise.

After graduating from the Harvard Medical School with honors he became an intern in the newly established Peter Bent Brigham Hospital, but although he is still listed among the distinguished alumni of that institution the truth is that after a week or so, bored by the humdrum tedium that is a pup's lot, he left for good.

He came to the Mallory Institute in 1916, but in 1920 he left to work with Hans Zinsser (who once said Parker was the only medical genius in Boston), only to return to the Boston City Hospital in 1923 under the late F. B. Mallory, who revolutionized histologic technic and permitted no smoking before noon. On Dr. Mallory's retirement in 1932 Parker became his successor as pathologist-in-chief in the newly opened Mallory Institute, planned and equipped by his lifelong friend Robert Nye.

One of Dr. Mallory's great contributions was a carefully conceived and skillfully executed program for training men for a career in pathology. F. Parker, Jr., took up this training where Dr. Mallory left off, and throughout the breadth of the country one will find professors of pathology trained at the Mallory Institute under one or the other of these men; a similar system of training has now been set up in virtually every first-class pathology laboratory in the United States.

A gracious and charming man with a keen sense of humor, he is nevertheless shy and reticent and seldom appears in public. His fame as a pathologist and the fruits of his wisdom and knowledge have been diffused almost entirely by his writings

and by the many men who have studied under him. Parker has always been an unusually able teacher, and he has that rare ability of seeing through a maze of apparently unrelated or contradictory findings to the essential truth. His ability to compress into a few well chosen words a veritable mine of information is widely known but is fully appreciated only by those whose privilege it has been to discuss with him some difficult microscopical diagnosis or to sit in with him on clinicopathological conferences. It is then, incidentally, that one learns of his almost uncanny knowledge of clinical diagnosis — he who has practically never seen a patient on the wards. Soft-spoken by nature and by custom, rarely if ever speaking ill of any man, he possesses, for use on very special occasions, a gently scathing tongue (his voice is then almost a whisper), and those who know him well realize that the more loudly he yells the less he means it. To those who do not know him intimately his mien may seem a bit formidable. Once, when he stopped at a gas station on the way home, a young attendant started to fill the tank — but, on seeing the driver of the car, put the hose back on the hook and shouted: "Quick, Ben, your tame lion's outside; better go feed him."

And then there was the time when his chief secretary was idly chatting in the corridor with a friend, — as chief secretaries will, — when suddenly there was a rich baritone bellow: "Hey, you!" — at which the chief secretary went in to see what the Boss wanted. Later her somewhat appalled friend asked how in the world she knew whom he wanted. With justified pride she replied: "Oh, I'm the only one he'd bellow at like that."

A long life of service to the medical profession and to the public at large lies behind F. Parker, Jr. May a long life of happiness be ahead.

MALARIA IN VETERANS RETURNING FROM KOREA

A NOTICE has recently been circulated among all state and territorial health officers to the effect that significant numbers of Armed Forces personnel from Korea are experiencing attacks of vivax malaria after their return to this country. These attacks occur when the subjects are not under military supervision, that is, when they are on leave or after they are separated from the service. Presumably these infections were acquired last fall, although in some instances it is probable that symptoms were not manifested until this spring because of prolonged incubation or the effects of suppressive medications.

Dr. R. A. Vonderlehr, the medical director in charge of the Communicable Disease Center of the Public Health Service, urges practicing physicians to suspect malaria among patients who present signs and symptoms of this disease and who have been in Korea during the last year. Definitive diagnosis should be based on the demonstration of malaria parasites in laboratories that are approved for this procedure. The chances of discovering parasites are much better in thick blood films than in thin ones. When blood findings are positive, controversial or uncertain, it is requested that the slides be sent to the National Depository for Malaria Slides, Parasitology Laboratories, Communicable Disease Center, P. O. Box 185, Chamblee, Georgia, where they will be examined by nongovernmental consultants.

Treatment with antimalarial drugs that are now available, namely, chloroquine, pentoquine, chlorguanide and others, will alleviate symptoms promptly. Certain patients who receive full doses of these drugs will remain free from malaria, but others probably will relapse after weeks or months. Patients should be told of this possibility and advised to return for further medical treatment if symptoms recur. The likelihood of clinical reactivation becomes less with the passage of time; relapses are rare after the second or third attack. The properties of the more important antimalarial drugs, the indications for their most effective use, their dosages and their toxic effects have been summarized recently.*

To prevent the spread of malaria from these returned veterans, cases should be reported promptly to local health authorities so that residual insecticides may be applied to houses within a mile of parasite-positive persons if malaria vectors such as

*Cooper, W. C. Summary of antimalarial drugs. *Pub. Health Rep*, 64: 717-732, 1949. (This summary is obtainable as Reprint No. 2939 of the Public Health Reports from the Superintendent of Documents, United States Government Printing Office, Washington, D. C. Price, 10 cents.)

Anopheles quadrimaculatus or *A. freeborni* are known or found to be prevalent in the area.

It is believed that if competent diagnosis, adequate treatment, prompt reporting and preventive insecticiding are achieved, the present freedom of this country from endemic malaria will be maintained.

AFTER ONE HUNDRED AND FIFTY YEARS

VACCINATION with cowpox was the first, and is still the greatest, accomplishment of preventive medicine. Although its vast potentiality for protecting man from his worst enemy was promptly recognized by such wise Americans as Benjamin Waterhouse and Thomas Jefferson, years of painful experience were needed to teach the common man that universal vaccination is the only condition under which a community can enjoy protection against smallpox. It was half a century before Massachusetts became sufficiently convinced of this, in 1855, to enact its compulsory-vaccination law for public schools, and even this was not enforced until 1873, when smallpox killed 1700 citizens of Boston.

Since that time vaccination of the individual has come to be regarded as a reasonable contribution that each can make to the health of his community, just as his taxes are a reasonable contribution to its wealth. Of course there have always been tax dodgers, and so have there been those who expect health from a community, even though they refuse to make their fair contribution thereto. These hygienic tax dodgers have generally grouped themselves into religious or other organizations, but, whatever their scruples, the fact remains that they continue to be spongers of health.

Now there has arisen in some of our educational institutions (of all enlightened places) a willingness to close the official eye to this kind of tax dodging. We understand that groups who claim conscientious objection to vaccination on religious grounds are being granted freedom from that participation in the common health, although it continues to be required of others! That those concerned know not what they do is suggested by an inane provision whereby if the smallpox should break out in their college community the unvaccinated will voluntarily absent themselves or submit to vaccination. A better arrangement than this for automatically closing a barn door behind a horse thief has yet to be devised, for if smallpox comes it will be the conscientious objector who brings it.

It is ironic that this should happen near Boston. Seismographic instruments in the area may well record the turning in their graves of Zabdiel Boylston, Ebenezer Roby, Cotton Mather, Benjamin Waterhouse, Horatio Adams, Samuel B. Woodward, Benjamin White and George H. Bigelow. Any spreading of the custom will be viewed with dismay by the health authorities of the Commonwealth, for, as Santayana said, "Those who cannot remember the past are condemned to repeat it."

They are copying, in Canada, the bad policy of their neighbors in the States, and have already organized too many medical colleges there. One is enough, but there are believed to be four, and more in embryo. This process of dilution with us has taught the unwelcome truth, that power lies in a concentration of forces.

Boston M. & S. J., *September 17, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHRISTIAN — Henry A. Christian, M.D., of Brookline, died on August 24. He was in his seventy-sixth year.

Dr. Christian received his degree from Johns Hopkins University School of Medicine in 1900. He was Hersey Professor of Medicine, emeritus, at Harvard Medical School and physician-in-chief, emeritus, of Peter Bent Brigham Hospital.

He was a fellow of the American Academy of Arts and Sciences, a master of the American College of Physicians, an honorary fellow of the Royal College of Physicians and a former president of the American Society for Clinical Investigation and of the Association of American Physicians. He was a member of the American Association of Pathologists and Bacteriologists, the American Medical Association, the Boston Medical Library, the American Society of Experimental Medicine, The Country Club and the Harvard Club of Boston.

His widow survives.

REARDON — John P. Reardon, M.D., of Cohasset, died on August 27. He was in his fifty-first year.

Dr. Reardon received his degree from Harvard Medical School in 1929. He was a staff member of the South Shore Hospital, Weymouth. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and two sons survive.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Muscular Contraction: A topic in molecular physiology. By W. F. H. M. Mommaerts, Ph.D. 8°, cloth, 191 pp., with 13 illustrations and 1 plate. New York: Interscience Publishers, Inc., 1950. $4.20.

This monograph deals with the metabolism of muscle and the muscle proteins and their relation to muscular activity. The pertinent literature is discussed throughout the text. There is a bibliography of 356 references. There is a good index. The book should be in all collections on physiology.

The External Secretion of the Pancreas. By J. Earl Thomas, M.D., professor of physiology, Jefferson Medical College of Philadelphia. 8°, cloth, 149 pp., with 22 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $3.50. Publication Number 45, American Lecture Series.

The text of this monograph constitutes a survey of the knowledge of the subject. The various chapters discuss the morphology of the pancreas, experimental methods, pancreatic juice, functions of the external secretion, stimuli for the pancreas, secretin and pancreozymin, functional innervation of the pancreas and the mechanism of pancreatic secretion. The various chapters are documented with lists of references. There are indexes of authors and subjects, and the text is lithoprinted. The monograph should be in all collections on physiology.

Publicaciones del Centro de Investigaciones Tisiologicas. Vol. XIII. Director: Prof. Roque A. Izzo. 4°, paper, 257 pp., with illustrations. Buenos Aires: Pabellon "Las Provincias," 1949.

The special volumes on the investigation of tuberculosis are an important series and should be in all collections on the subject. The present volume contains nine studies, including the rehabilitation and readaptation of the cured tuberculous patient in the United States, streptomycin, the treatment of tuberculosis, the pleural and pulmonary manifestations in granulomatosis maligna, histoplasmosis and pulmonary calcifications, the presence of histamine in the central nervous system, hypertension and the chemistry of Vitamin A and the carotenes.

Skull Fractures and Brain Injuries. By Harry E. Mock, M.D., consulting surgeon, St. Luke's Hospital, Chicago. 8°, cloth, 806 pp., with 116 illustrations. Baltimore, Maryland: The Williams and Wilkins Company, 1950. $13.50.

This new work is based on the author's experience of forty years in the field of surgery of injuries and diseases of the skull and their complications. The subject is covered thoroughly, with emphasis on diagnosis and treatment. There are chapters on extradural hematoma, subdural hemorrhage, post-traumatic epilepsy and cranial-nerve injuries, and a chapter on the eye in craniointracranial injuries by Dr. R. C. Gamble. A bibliography of selected references concludes the text. The book is well published and should be in all medical libraries and in the collections of surgeons and neurologists interested in the subject.

Encyclopedia of the Eye: Diagnosis and treatment. By Conrad Berens, M.D., executive eye surgeon, New York Eye and Ear Infirmary, professor of clinical ophthalmology, New York University Post-Graduate Medical School, president, Pan-American Association of Ophthalmology, managing director of the Ophthalmological Foundation, Inc., and president, Snyder Ophthalmic Foundation, and Edward Siegel, M.A., M.D., attending ophthalmologist, Champlain Valley Hospital, Plattsburg, New York, and associate attending ophthalmologist, Physicians Hospital, Plattsburg. 12°, cloth, 272 pp., with 76 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $5.00.

This encyclopedia has been prepared for practical use as a ready reference manual on the diagnosis and treatment of diseases of the eye. The material is arranged alphabetically by subjects.

Fainting: Physiological and psychological considerations. By George L. Engel, M.D., associate professor of medicine and psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, New York. 8°, cloth, 141 pp., with 4 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.75.

This monograph discusses the causative factors that induce fainting, including the fall in arterial blood pressure, cardiac conditions, cerebral disturbances and disorders, fainting during air travel, syncope and differential diagnosis. The pertinent literature on the subject is surveyed, and there is a bibliography of 78 references. There are indexes of authors and subjects. This small book should be in all collections on clinical medicine.

Bronchoesophagology. By Chevalier Jackson, M.D., Sc.D., LL.D., and Chevalier L. Jackson, M.D., M. Sc., professor of bronchoesophagology and laryngeal surgery, Temple University, Philadelphia. 4°, cloth, 366 pp., with 260 illustrations. Philadelphia: W. B. Saunders Company, 1950. $12.50.

This new book of the Doctors Jackson replaces their former textbook on bronchoscopy and esophagoscopy, which exhausted three editions and was translated into four foreign languages. The text has been brought up to date, reflecting the present knowledge of the subject. The book is divided into two parts: bronchology and esophagology. There is an appendix on the instruments needed for peroral endoscopy. A bibliography of 429 references is appended to the text; there is a comprehensive index. The publishing is excellent. This new book by the outstanding authorities in their field is recommended for all medical libraries and to all physicians interested in the subject.

Clinical Studies in Psychoanalysis. By Sandor Lorand, M.D., professor of clinical psychiatry (psychoanalytic medicine), director of psychoanalytic clinic, State University Medical Center at New York College of Medicine. 8°, cloth, 272 pp. New York: International Universities Press, Inc., 1950. $4.00.

Dr. Lorand in this book has brought together for easy reference eighteen papers previously published in various periodicals. There is a bibliography of 141 references, and a good index. A number of the papers have to do with sexual subjects.

Savill's System of Clinical Medicine: Dealing with the diagnosis, prognosis and treatment of disease. For students and practitioners. Edited by E. C. Warner, M.D., F.R.C.P. Thirteenth edition. 8°, cloth, with 202 illustrations and 61 tables. Baltimore: The Williams and Wilkins Company, 1950. $7.00.

Dr. Savill's textbook of medicine, first published over fifty years ago, has now become the joint work of eighteen well known British physicians. The whole field of clinical medicine is covered, and there are chapters on the nervous system, psychologic disorders, the examination of pathologic fluids and clinical bacteriology. There is a comprehensive index, and the publishing is excellent. The printing was done in Great Britain.

The Hebrew Impact on Western Civilization. Edited by Dagobert D. Runes. 8°, cloth, 922 pp. New York, New York: Philosophical Library, Inc., 1951. $10.00.

This book is the composite work of 17 authors, and attempts to bring to the present generation the story of the life and work of the Jewish people from their beginnings to the present. Dr. Solomon R. Kagan of Boston writes on the influence of the Jew on modern medicine, A. A. Roback on the Jew in modern science. This last contribution by a well known authority constitutes a monograph in itself and con-

tains much material of medical interest concerning anatomy, physiology and bacteriology. There is a comprehensive index; the book is well published.

Grundlagen der Gynäkologie: Funktionelle Anatomie, Regulationsvorrichtungen Untersuchungstechnik. Für Studenten, Ärzte und Fachärzte. Von Prof. Dr. Med. Heinrich Martius, Direktor der Univ.-Frauenklinik Göttingen. 4°, cloth, 144 pp., with 113 illustrations. Stuttgart: Georg Thieme, 1950. $5.55. Distributed by Grune and Stratton, Inc., New York.

This manual on the fundamentals of gynecology is divided into three parts — on the growth and function of the female sexual organs, on the female sexual functions and on special gynecologic examination technic. There is a bibliography and a good index, and the publishing is excellent.

Die Funktionellen Sexualstörungen: Einführung in die Entstehungsbedingungen, Erscheinungsformen, Arkennung, Beurteilung und Behandlung der Störungen der Libresfähigkeit. By Werner Kemper. 8°, paper, 102 pp. Stuttgart: Georg Thieme, 1950. $1.35. Distributed by Grune and Stratton, Inc., New York.

This small monograph is well written, and the material is well arranged. The text is divided into two parts. The first discusses the subject in general. Part Two presents comprehensive studies of six cases of functional sexual disturbances in five categories. The publishing is excellent, and the monograph should be in all collections on the subject.

Praktikum der Wichtigsten Infektionskrankheiten. Von Prof. Dr. C. Hegler. Bearbeitet von Prof. Dr. H. E. Bock, Direktor der Medizinischen Universitätsklinik Marburg (Lahn). Fifth edition. 8°, cloth, 277 pp. Stuttgart: Georg Thieme, 1950. $3.50. Distributed by Grune and Stratton, Inc., New York.

The first edition of this practical manual on infectious diseases was first published in 1934. The fifth edition has been revised and brought up to date; new material has been added on the influenza viruses A and B, hepatitis epidemica, meningitis and encephalitis, lymphogranuloma inguinale and other diseases due to infection. The last chapter discusses treatment with sulfonamides, penicillin and streptomycin. There is a good index, and the publishing is excellent. The manual should prove valuable to German-reading physicians.

Leitfaden für den Geburtshilflichen Operationskurs. Von Dr. med. et Dr. art. obst. h. c. Albert Döderlein. Twentieth edition. 8°, paper, 272 pp., with 184 illustrations. Stuttgart: Georg Thieme, 1950. $1.80. Distributed by Grune and Stratton, Inc., New York.

The first edition of this popular manual on delivery was published in 1893, and succeeding editions have been revised to keep the material up to date. There is a good index, and the publishing is excellent.

Hirndurchblutungsstörungen: Ihre Klinik und arteriographische Diagnose. Von A. Brobeil, Dozent an der Universitäts-Nervenklinik Marburg-Lahn. 4°, cloth, 264 pp., with 84 illustrations. Stuttgart: Georg Thieme, 1950. Ganzleinen DM 45.- Distributed by Grune and Stratton, Inc., New York.

This monograph on hemorrhagic disturbances of the brain is well published, and the illustrations are excellent. The text is divided into seven parts: on the pathologic physiology of the brain circulation, the arterial supply of the cerebrum and the clinical prolapse syndrome, the blood supply of the pons and medulla oblongata, embolism and thrombosis, cerebral-vessel crises, cerebral thromboangiitis obliterans and cerebral sclerosis. There are ten pages of references appended to the text, and there is an index of subjects. The book should be in all collections on the brain and circulatory system.

Monographs on Surgery, 1951. Edited by B. Nolan Carter, M.D., Ph.D., professor of surgery, University of Cincinnati, and director of surgical services, Cincinnati General Hospital. 8°, cloth, 508 pp., with illustrations. New York: Thomas Nelson and Sons, 1950. $12.50.

This second volume of the surgical monographs contains seventeen articles by twenty-two contributors on various subjects. Included are five articles on carcinoma in situ of the cervix, one on the cytologic diagnosis of cancer and a group of four articles on bone and joint conditions. Boston is well represented by eight contributors. The volume is well published, and the series should be in all medical libraries.

Medical Treatment in Obstetrics and Gynecology. By C. Frederic Fluhmann, M.D., C.M., clinical professor of obstetrics and gynecology, Stanford University School of Medicine, assistant visiting obstetrician and gynecologist, Stanford-Lane Hospitals, and courtesy staff, St. Francis and Mount Zion Hospitals, San Francisco, California. 8°, cloth, 157 pp., with 27 illustrations. Baltimore, Maryland: The Williams and Wilkins Company, 1951. $3.00.

This manual is designed for quick reference to material used in everyday practice. The text is divided into four parts: diagnosis and medical therapy, therapeutics, nutrition and office and hospital procedures. The small volume is well published, and there is a good index.

Pulmonary Ventilation and its Physiological Regulation. By John S. Gray, M.D., Ph.D., professor of physiology, Northwestern University Medical School. 8°, cloth, 82 pp., with 14 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00. (Publication Number 63, American Lecture Series.)

This monograph discusses the phase of pulmonary ventilation in which oxygen and carbon dioxide are interchanged.

Psychotherapy. By Paul Schilder, M.D., Ph.D. Enlarged and revised edition arranged by Lauretta Bender, M.A., M.D., associate professor of psychiatry, New York University College of Medicine, associate attending psychiatrist, New York University-Bellevue Medical Center, and senior psychiatrist, Bellevue Hospital. 8°, cloth, 396 pp. New York: W. W. Norton and Company, Inc., 1951. $5.00.

This new edition of a well known book, first published in 1938, has been revised by Dr. Bender, a co-worker of Dr. Schilder for four years before his death in 1940. The revision has been limited to the addition of articles or excerpts of articles of a pertinent nature published prior to 1940. The editor has made no original contributions to the text but has added a number of footnotes. The book is well published and should be in all collections on psychotherapy.

Symposium on the Healthy Personality: Transactions of special meetings of conference on infancy and childhood June 8-9 and July 3-4, 1950, New York, New York. Edited by Milton J. E. Senn, M.D., departments of Pediatrics and Psychiatry, Yale University School of Medicine. 8°, cloth, 298 pp. New York: Josiah Macy, Jr., Foundation, 1950. $2.50. Supplement II: Problems of Infancy and Childhood, Transactions of fourth conference, March, 1950.

The conferences were devoted to three main topics: growth and crises of the healthy personality, constitutional and prenatal factors in infant and child health, and social psychology of mental health. The conferences were attended by eighteen members and twenty guests. Dr. Frank Fremont-Smith outlined the Foundation conferences program.

Metabolic Interrelations: Transactions of the second conference, New York, New York, January 9-10, 1950. Edited by Edward C. Reifenstein, Jr., M.D., Sloan-Kettering Institute, New York. 8°, paper, 279 pp., with 67 illustrations and 44 tables. New York: Josiah Macy, Jr., Foundation, 1950. $3.95.

Twenty-five experts in their particular fields took part in the conference; eleven papers were read on various aspects of the subject. The Macy Foundation publications should be in all medical libraries. They are fundamental research source material.

Diathermy: The use of high frequency currents. By Stafford L. Osborne, M.S., Ph.D., chairman, Department of Physical Medicine, Northwestern University Medical School. 8°, paper, 113 pp., with 63 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $3.00. (Publication Number 91, American Lecture Series.)

This short monograph discusses the use of high-frequency currents in treatment, and its contraindications. There is a short chapter on surgical diathermy. The illustrations are excellent. The book is not intended as a treatise but rather as a manual for the medical student, physical therapist and general practitioner.

The Science of Health. By Florence L. Meredith, M.D. Second edition. 8°, cloth, 452 pp., with 134 illustrations and 48 tables and charts. Philadelphia: The Blakiston Company, 1951. $3.75.

This second edition of a textbook for teachers of hygiene has been revised and brought up to date. A bibliography is appended to the text, and there is a good index. The publishing is good. The book will well serve the purpose for which it is intended.

Physical Diagnosis. By Ralph H. Major, M.D., professor of medicine, University of Kansas. Fourth edition. 8°, cloth, 446 pp., with 469 illustrations. Philadelphia: W. B. Saunders Company, 1951. $6.50.

This fourth edition of a standard textbook has been revised, and new material and illustrations have been added. Lists of references have been added to the various chapters, and there is a good index. The publishing is excellent.

Therapie des Diabetes Mellitus: Ein Leitfaden für praktische Ärtze und Studenten der Medizin. Von Dr. Med. Georg R. Constam. 8°, cloth, 291 pp., with 16 illustrations. Basel, Switzerland: Benno Schwabe and Company, 1950. Gebunden Fr. 16.50. Distributed by Grune and Stratton, Inc., New York.

The title of this new book on diabetes is rather misleading, as the text covers the various aspects of the disease from carbohydrate metabolism through complications, diabetes in pregnancy and surgery of diabetes. Lists of references, some lengthy, are appended to the various chapters — nineteen in all. The pertinent literature of all countries is discussed throughout the text. Reference is frequently made to the work of Dr. Joslin and his associates. There is an index, and the book is well published. It should be in all collections on the subject.

Neurology and Psychiatry in General Practice. Edited by Henry R. Viets, M.D., in collaboration with C. Charles Burlingame, M.D., Clarence B. Farrar, M.D., and Z. M. Lebensohn, M.D. 8°, cloth, 150 pp. New York: Grune and Stratton, Inc., 1950. $3.50.

In this volume are presented papers by well known specialists on various topics of interest to the general practitioner. The papers were read and discussed by 33 physicians at a three-day symposium held during the midwinter meeting of the American Medical Association in 1949. The topics were first selected and then men were found who were best suited to develop the subjects. The material is about evenly divided between the two fields of neurology and psychiatry. This symposium was the first venture of its kind and had the full support of the late Dr. C. Charles Burlingame, to whom the book is dedicated. The material is ably edited by Dr. Viets. The publishing is excellent, and the book should prove of practical value to the practicing physician.

I Vizi Della Mitrale: Note statistico-nosografiche e fisiopatogenetiche su mille osservazioni. By Angelo Luciani. Preface by Prof. C. Cassano. 8°, paper, 157 pp., with 23 illustrations. Pisa: Omnia Medica, 1950. $3.50.

This comprehensive monograph on mitral disease of the heart is based on a study of 1000 cases. In the text is discussed the pertinent literature of all countries on the subject, including that of Dr. Paul Dudley White of Boston. The predominance of rheumatic infection as an etiologic factor is stressed. Nearly 50 per cent of the 1000 cases were due to rheumatism. A bibliography of 192 references is appended to the text. The monograph is of distinct reference value, and should be in all collections on the heart.

The 1950 Year Book of Drug Therapy (October, 1949–September, 1950). Edited by Harry Beckman, M.D., director, Department of Pharmacology, Marquette University School of Medicine. 12°, cloth, 566 pp., with 88 illustrations. Chicago, Illinois: Year Book Publishers, Inc., 1951. $5.00.

This yearbook covers the literature on drug therapy for the year ending September, 1950. There are indexes of subjects and authors. The book should be in all current medical reference collections.

Trephine Technique of Bone Marrow Infusions and Tissue Biopsies. By Henry Turkel, M.A., M.D. Fourth edition. 8°, paper, 60 pp., with illustrations. Detroit, Michigan: Gale Printing Company, 1950. $1.00.

This small technical manual has now gone into its fourth edition. A bibliography of 15 pages is appended to the text. In future editions an index would be appreciated.

NOTICES

ANNOUNCEMENT

Dr. Frederic Hertzmark announces the removal of his office for the practice of pediatrics and pediatric allergy to 1246 Blue Hill Avenue, Mattapan.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The next meeting of the Middlesex South District Medical Society will be held at the Mount Auburn Hospital, Cambridge, on Wednesday, October 17, at 11:30 a.m.

SOCIETY MEETINGS AND CONFERENCES

September 17–19. National Gastroenterological Association. Page 350, issue of August 30.

September 19. American Medical Writers' Association. Page 1066, issue of December 28.

September 19. New England Pediatric Society. Page 388, issue of September 6.

September 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

September 26. Massachusetts Academy of General Practice. Page 388, issue of September 6.

September 30–October 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.

October 9. Springfield Academy of Medicine. Page 350, issue of August 30.

October 17. Middlesex South District Medical Society. Notice above.

October 20–25. American Academy of Pediatrics. Royal York Hotel, Toronto, Ontario, Canada.

October 22–24. American Association of Blood Banks. Page 316, issue of August 23.

October 22–27. Medico-Military Symposium. Page 234, issue of August 9.

October 29. New York Institute of Clinical Oral Pathology. Page xv, issue of June 14.

October 29–November 2. American Public Health Association. Page 316, issue of August 23.

October 31. New England Obstetrical and Gynecological Society, Hotel Somerset, Boston.

November 2 and 3. Eastern Section, American Trudeau Society. Page 350, issue of August 30.

November 4 and 5. American Society for the Study of Arteriosclerosis. Page xv, issue of July 12.

November 5–9. American College of Surgeons. Page 388, issue of September 6.

November 7–19. Pan-Pacific Surgical Association. Page 820, issue of May 24.

December 11–19. International Congress on Mental Health. Page xiii, issue of July 26.

December 14 and 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

(*Notices concluded on page xix*)